The American Journal of Medicine

December 1951

The American Journal of Medicine

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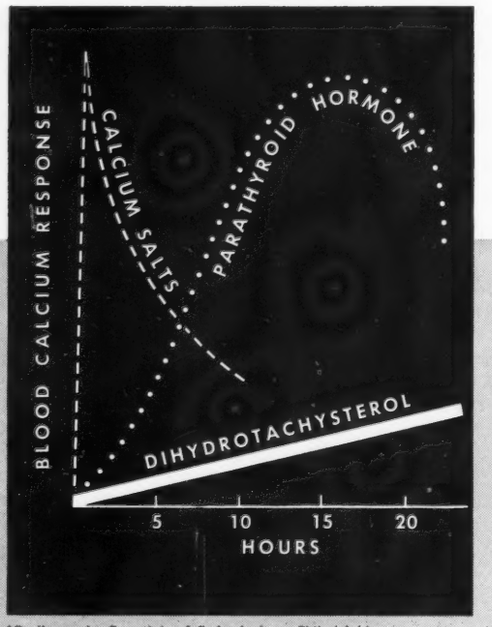

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*Grollman, A.: Essentials of Endocrinology. Philadelphia, J. B. Lippincott Co., 1947, 2nd ed., p. 269.

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Editorial

Clinical Studies

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Anxiety and Autonomic Lability as the Basis of Functional Disorders

Emotional response to the stress of life is the primary source of illness in a steadily increasing number of cases. *Weiss* and *English*[1] estimate that as high as two-thirds of all patients have disorders due either entirely or in part to emotional factors and anxiety. *Ebaugh*[2] refers to anxiety as ". . . the universal disease of our times".

Complete examination discloses no organic basis for the symptoms in these cases, yet the clinical picture may mimic a true organic disease.

The symptom-complex usually involves several organ systems.[2,3,4] In such cases, the anxiety is channeled into organ dysfunction via the autonomic nervous system.[2,3,5,6] Some of the effects produced by exaggerated activity of a labile autonomic system are tabulated below. Many of these, it will be noted, are related to the symptoms which feature prominently in functional disorders. The symptoms in any one case are not necessarily limited to one organ system. Usually some are referable to sympathetic hypertonicity, others to parasympathetic hypertonicity.

ORGAN SYSTEM	SYMPATHETIC HYPER-TONICITY	PARASYM-PATHETIC HYPER-TONICITY	SYMPTOMS OF FUNCTIONAL DISORDER	AUTONOMIC LABILITY
GASTRO-INTESTINAL	Hypomotility Hyposecretion Intestinal Atony	Increased Salivation Hypermotility Hypersecretion	Belching Heartburn Nausea & vomiting Mucous diarrhea	When a patient exhibits a clinical picture suggestive of non-organic dysfunction, the diagnosis of Functional Disorder can be facilitated by use of the following indications of Autonomic Lability: Variable Blood Pressure Temperature Variations Changing Pulse Rate Deviations in B.M.R. Exaggerated Cold Pressure Reflex Oculo-cardiac Reflex Abnormalities Glucose Tolerance Alterations
CARDIO-VASCULAR	Rapid heart rate Peripheral vaso-constriction Slight rise in blood pressure	Reduced heart rate Vasodilatation Lowered blood pressure	Palpitation Sinus tachycardia Premature systoles B.P. low in some; elevated in others	
RESPIRATORY	Dry nasopharyngeal mucous membrane Bronchial relaxation	Increased nasopharyngeal secretion Bronchial constriction Laryngospasm	Dry mouth and throat Difficulty in breathing Sighing respiration	
GENITO-URINARY	Bladder detrusor relaxed; Sphincter contracted Ureter tone and motility decreased	Bladder detrusor contracted; Sphincter relaxed Ureter tone and motility increased	Urinary frequency Difficulty in urinating Dysmenorrhea Menstrual irregularity	

This tabulation is based on data available in references 1 to 6 stated below.

Primarily, the patient visits his physician out of concern over his symptoms. At this point, he is either unaware of his basic emotional problem or ignores it. A complete examination will rule out organic disease and thus reassure the patient. Then, treatment is directed along two lines: First, relieve the patient of subjective distress by drug therapy.* He will then be more cooperative in discussing his emotional problems. Then, having uncovered the basic problem, guidance is given toward correcting unhealthy situations and attitudes.

*The fact that autonomic dysfunction plays a large part in mediating the disturbance suggests autonomic sedation. A number of independent studies indicate that this therapeutic approach is effective.[7,8,9] The investigators used ergotamine tartrate (adrenergic blockade), levo-alkaloids of belladonna (cholinergic blockade) and phenobarbital (central sedation) in the form of **Bellergal** tablets. The total effect is an integrated sedation of the entire A.N.S.

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Case Reports

Advertising Index on 3rd Cover

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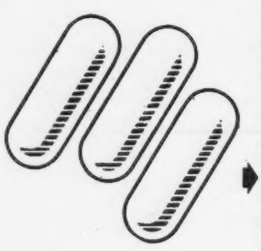

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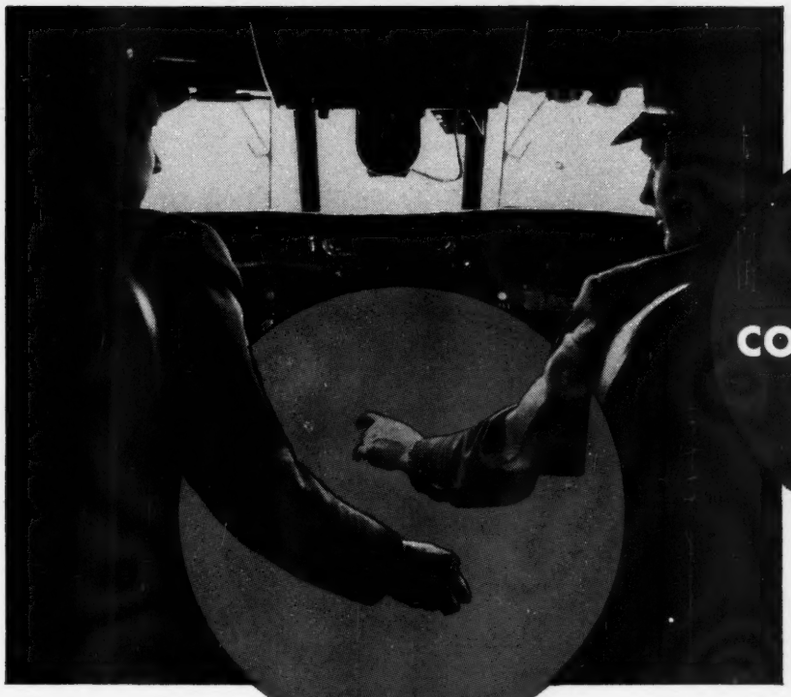
Folic Acid	3.6 mg.
Stomach-Liver Digest	1.5 Gm.

*MDR—Minimum Daily Requirement
†RDA—Recommended Daily Dietary Allowance



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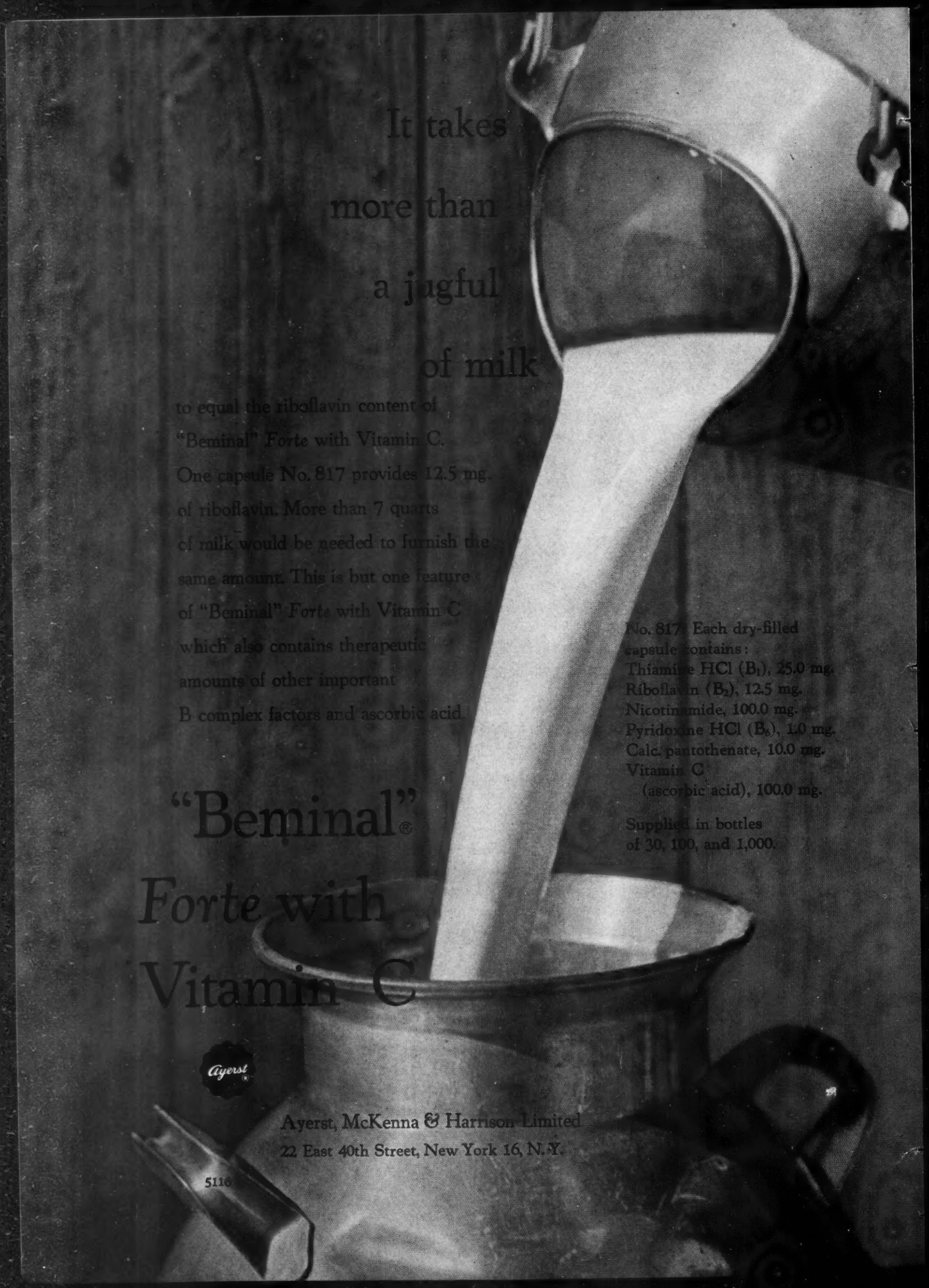
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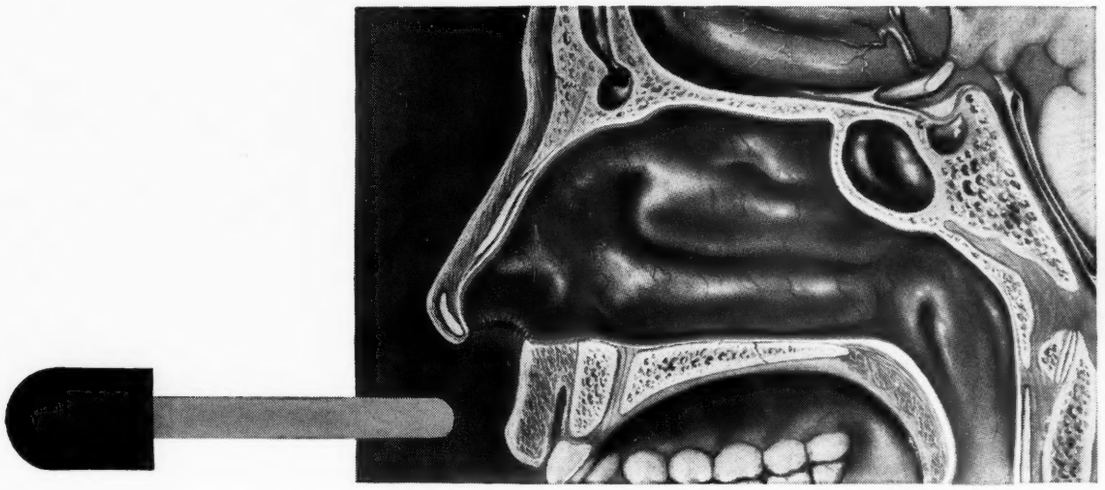

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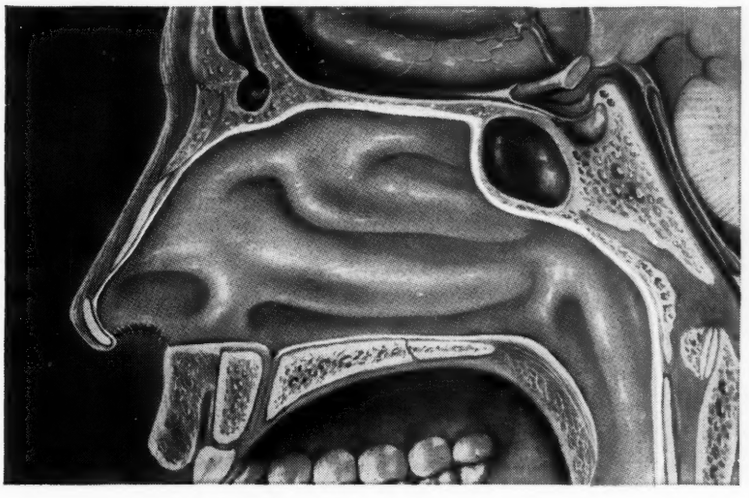

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---

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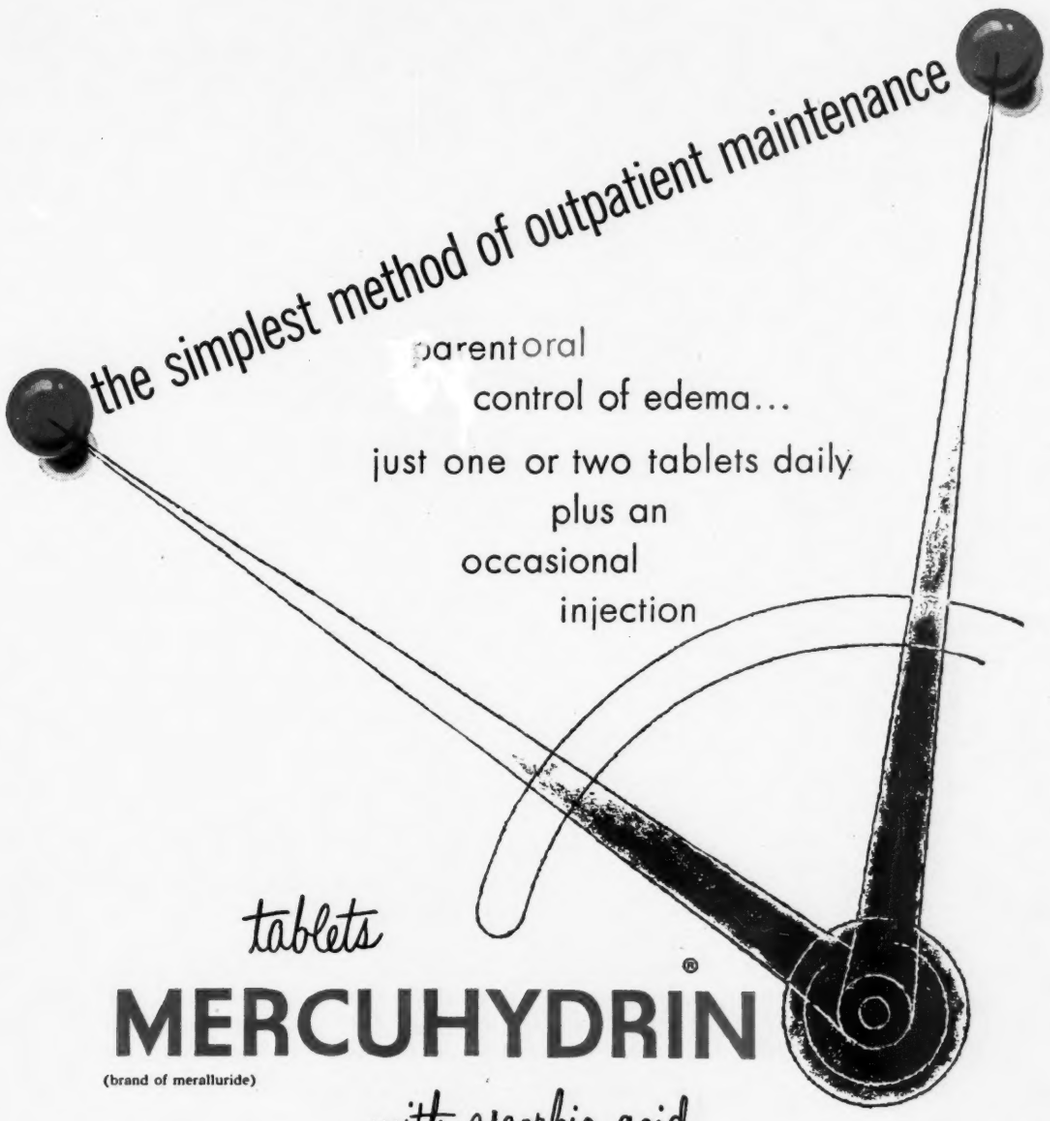

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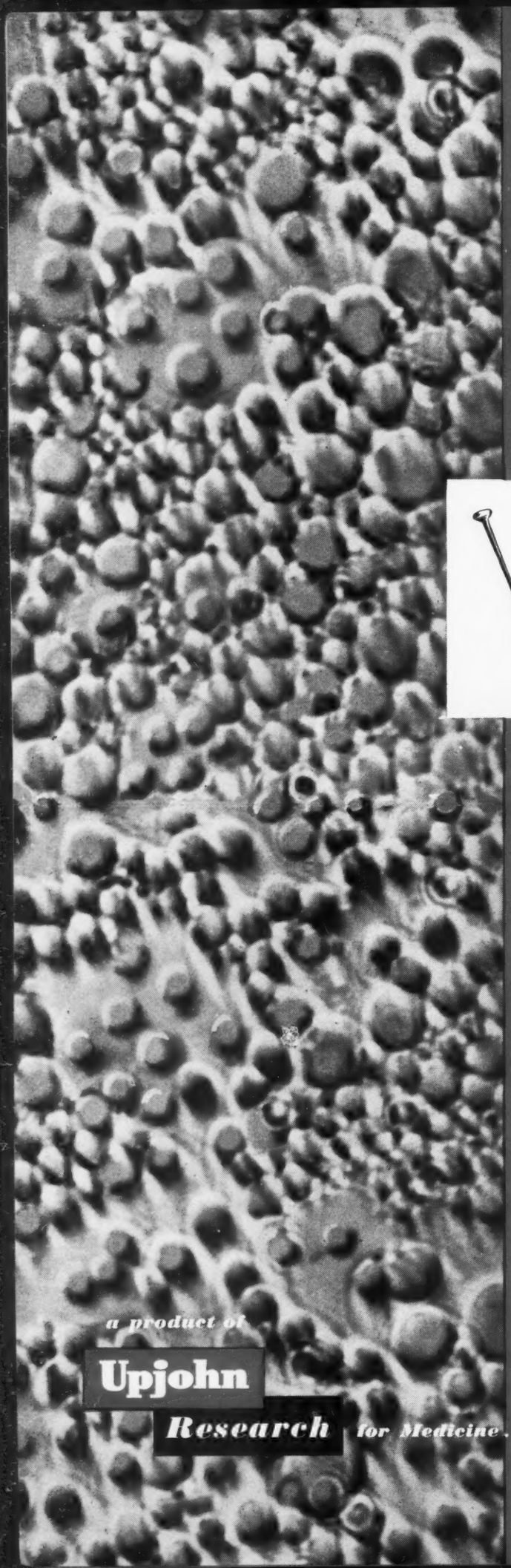

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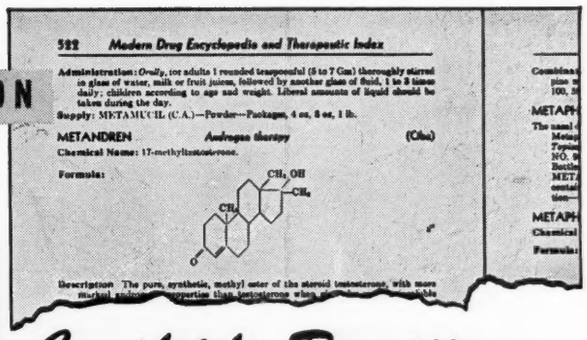
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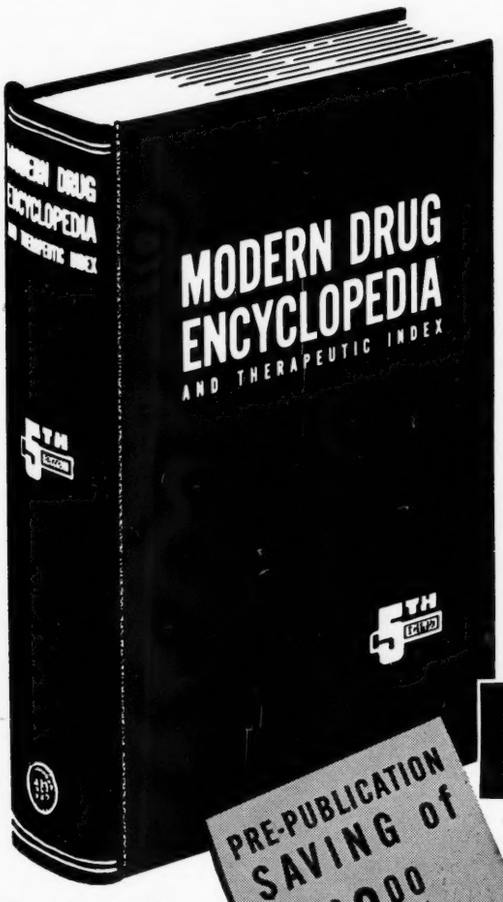

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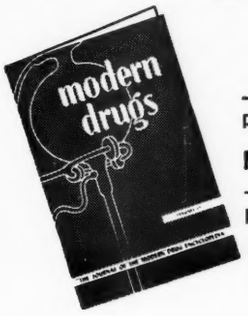

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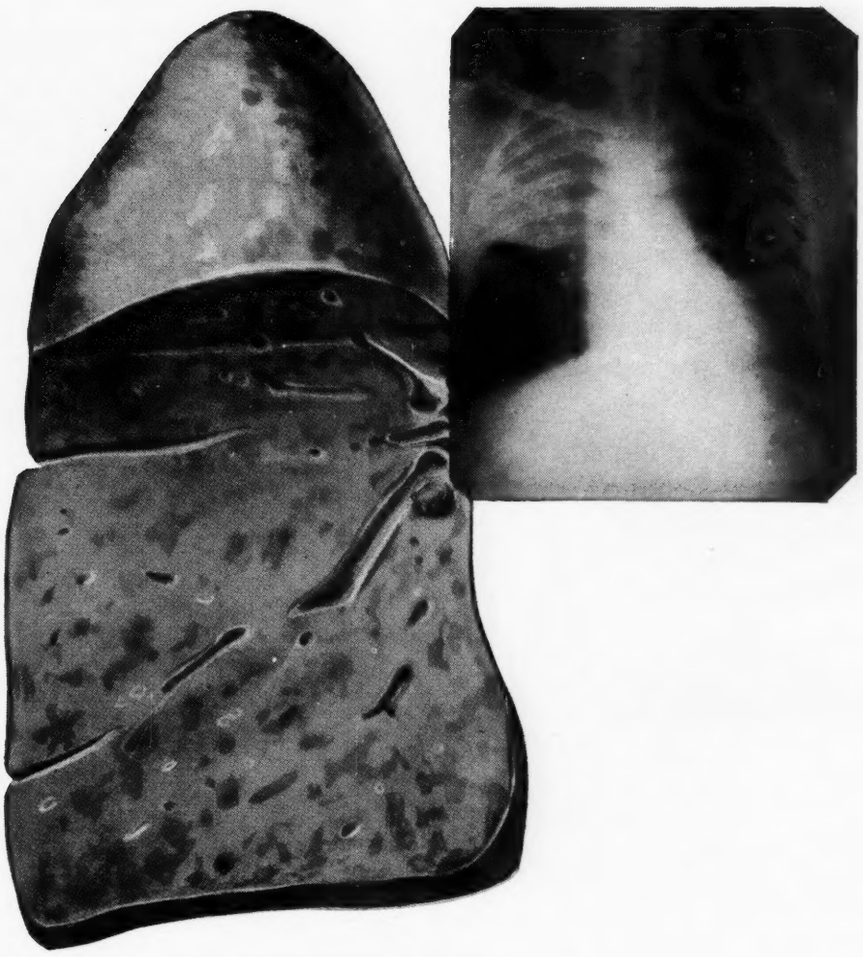

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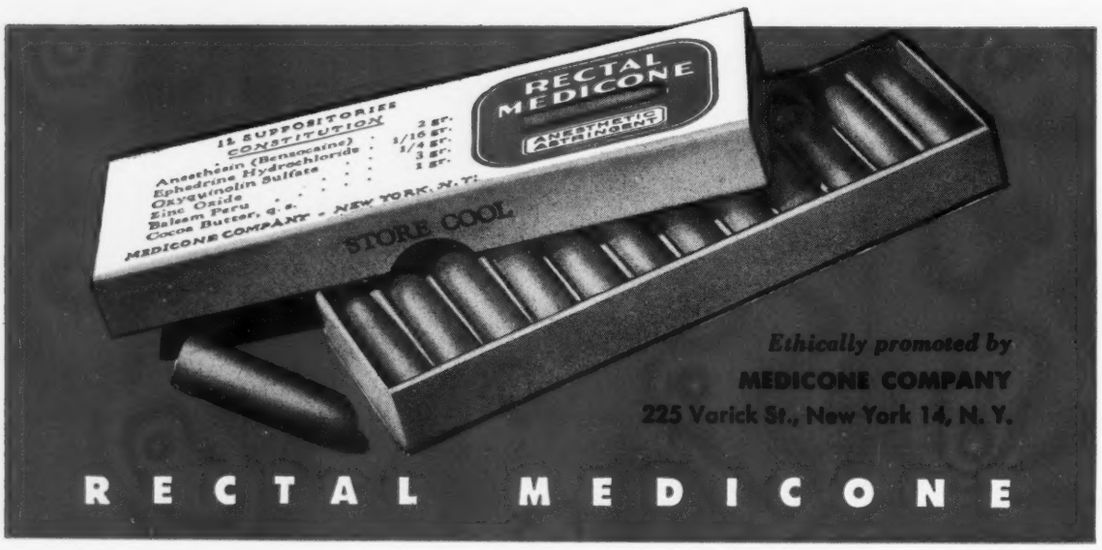

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REFERENCES: 1. Dry, T. J. et al.: Proc. Staff Meetings Mayo Clin., 21:497, 1946. 2. Hoagland, R. J.: Am. J. Med., 9:272, 1950. 3. Smith, R. T.: J. Lancet, 70:192, 1950.

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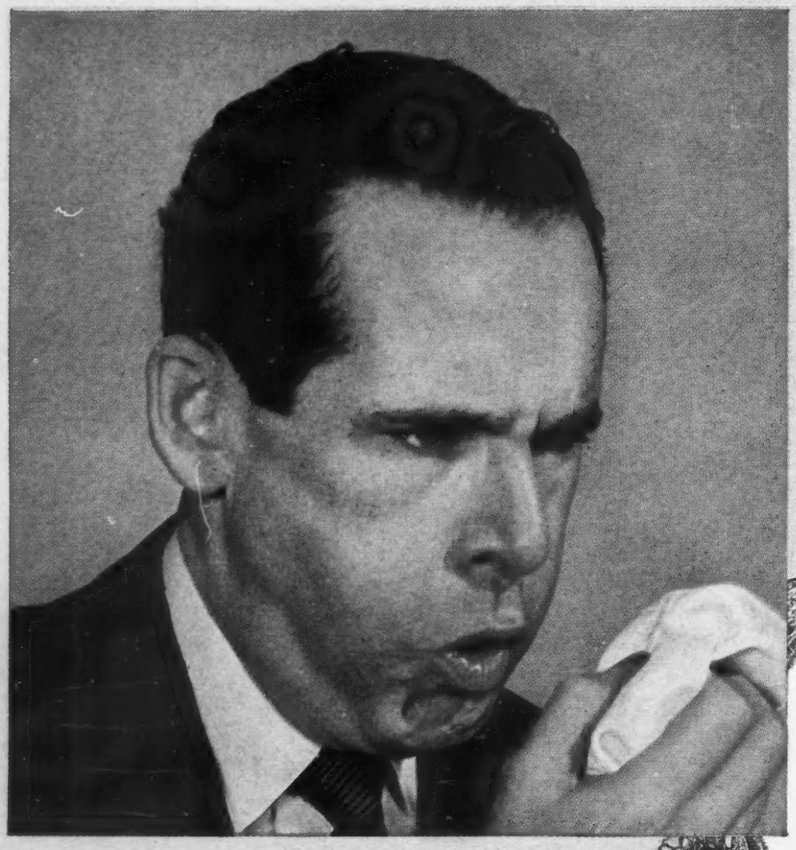

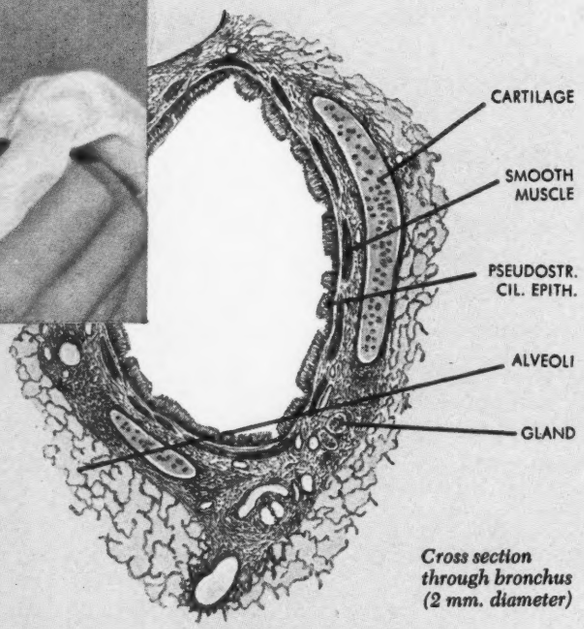

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References:

1. Boyd, E. M. and Lapp, S.: J. Pharmacol. and Exper. Therap., 87:24, 1946. 2. Connell, W. F. et al.: Canad. M.A.J., 42:220, 1940. 3. Novelli, A. and Tainter, M. L.: J. Pharmacol., 77:324, 1943.

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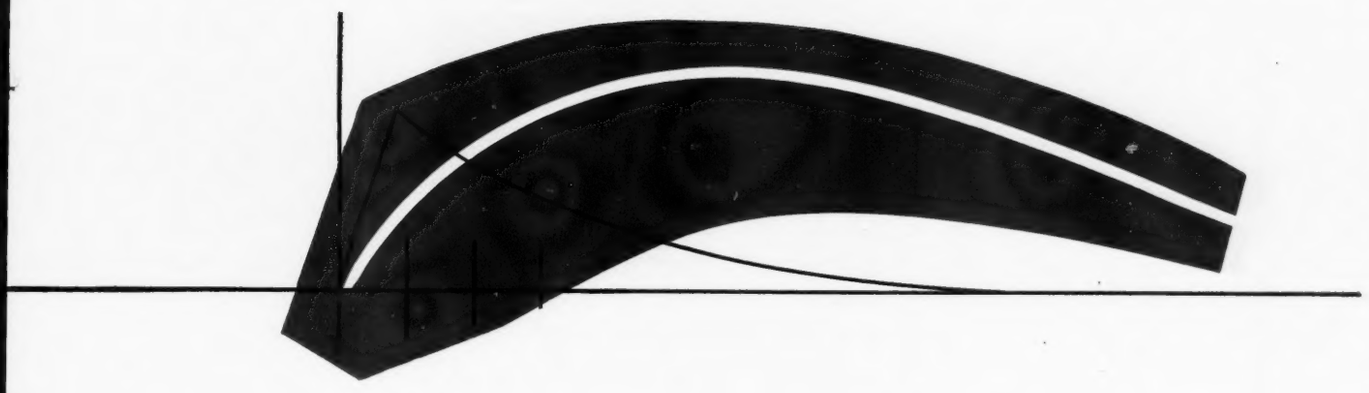

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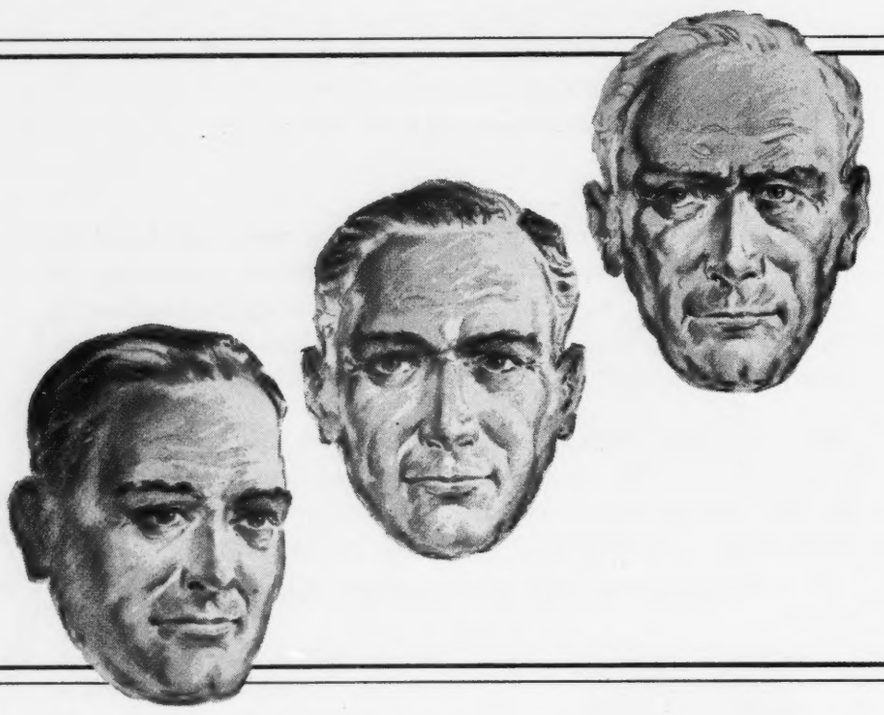

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The American Journal of Medicine

VOL. XI DECEMBER, 1951 NO. 6

Editorial

Alterations in Normal Bacterial Flora of Man and Secondary Infections during Antibiotic Therapy

IT is now firmly established that striking alterations in the bacterial flora in various regions of the body may occur following the use of antibiotics.[1–3] This change in the bacterial flora is independent of the effect of the antibiotic on the specific organism responsible for an infection. Thus when penicillin is given, susceptible and sensitive gram-positive bacteria may be eliminated from the mouth and nasopharynx and only non-sensitive and gram-negative organisms can be isolated. When streptomycin is administered, susceptible gram-negative organisms disappear and only gram-positive organisms survive. Following the exhibition of aureomycin, terramycin or chloramphenicol all of the susceptible gram-positive as well as gram-negative organisms may disappear, leaving only monilia, or other non-sensitive bacteria or yeasts. In any event it appears that the surviving bacteria will depend upon the susceptibility of the microorganisms in the original flora, the development or appearance of resistant strains or the introduction of new and resistant strains of microorganisms from outside.

In many instances these changes in the local bacterial flora are unimportant and inconsequential; thus they would fail to attract attention unless careful bacteriologic cultures were made. In other cases, however, a new infection appears. These new infections may arise in one of several ways. (1) New organisms may be introduced from outside, i.e., from carriers or from contact with other infections, or by the accidental introduction of new organisms during the manipulations incident to proper administration of the antibiotic agent. (2) Organisms which are present in small numbers and which are not sensitive to the antibiotic may flourish and invade tissues after the susceptible organisms are inhibited. (3) Organisms appear rapidly which have become resistant after exposure to an antibiotic.

Weinstein[4] has reported cases of staphylococcic pneumonia, bacteremia and pyelonephritis due to staphylococci in patients who had an original Hemophilus influenzae infection and who were treated with streptomycin. A number of other observers have reported oral, intestinal, bronchopulmonary, genital, dermal and generalized infections due to monilia[5] following the

[1] LIPMAN, M. O., COSS, J. A. and BOOTS, R. H. Changes in bacterial flora of the throat and intestinal tract during prolonged oral administration of penicillin. *J Bact.*, 51: 594, 1946.

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use of penicillin, aureomycin, chloramphenicol and terramycin therapy. Finland[6] records instances of staphylococcic diarrhea in patients receiving terramycin, and Weinstein and his associates[7] have recently called attention to the high incidence of suppurative otitis media and bronchopneumonia in patients with pertussis who received either aureomycin or chloramphenicol. Also, Chang and Jackson[8] have noted scarlet fever due to hemolytic staphylococcus aureus infections following the treatment of pertussis with the broad spectrum antibiotics, or the use of prophylactic penicillin for the treatment of a burn. These are a few of the new or superimposed infections that have been reported following antibiotic therapy, and they only serve to point up this important problem. It is necessary for all physicians to be alert to the problem and to continue to study this complex phenomenon so that ways and means may be found to prevent new infections as well as treat them when they arise. Bacteriologic studies continue to remain important in the treatment of patients with infectious diseases because new or resistant infections can be recognized only by following the changes in bacterial flora in various regions of the body.

CHESTER S. KEEFER, M.D.

MANNING, I. H., JR. and PATTERSON, C. N. Monilial infections complicating the therapeutic use of antibiotics. *J. A. M. A.*, 145: 207, 1951. GEIGER, A. J., WENNER, H. A., AXILROD, H. D. and DURLANDER, S. H. Mycotic endocarditis and meningitis. *Yale J. Biol. & Med.*, 18: 259, 1945.

[6] FINLAND, M. The present status of antibiotics in bacterial infections. *Bull. New York Acad. Med.*, 27: 199, 1951.

[7] Personal communication.

[8] Quoted by Finland.

Notice to Subscribers

THE following excerpt is representative of several letters that have been received requesting that the publishers of the *American Journal of Medicine* make available a complete index of past issues of the *Journal*.

"Since I left _____ Hospital in July 1948, the most instructive hours of postgraduate education have been those which I have devoted to reading *The American Journal of Medicine*. Faced with the problem of a comprehensive review for my American Board Examination, with the somewhat limited time at my disposal, I resorted to re-reading the issues of the *Journal* as my formal review exercise. This I found most profitable. Because my office is not in the same building as the local medical library, I frequently go back over the *Journal* for information on some particular topic, usually with productive results. In this regard I have often wondered whether you had ever considered the feasibility and practicality of printing a complete index every two years covering the preceding years' issues. This as I gather it would involve a considerable expense to the publishers. I have discussed the matter with a fair number of my colleagues in this city, all of whom felt they would be willing to pay for such an index in addition to the regular subscription fee.

"I hope that this does not seem like too harebrained an idea to you. I am sure you can understand it was prompted by the fact that the private practitioner, out of the hospital environment, is no longer able to assimilate by osmosis the many new ideas and facts that he did during his house officer days in the large teaching hospital."

(Signed) L. O. J.
R. M. W.
North Carolina

The Editorial Board and the publishers of *The American Journal of Medicine* are most anxious to make the contents of the *Journal* maximally available for teaching and review purposes, and have therefore decided to issue a complete index of articles and abstracts which appeared in the first five years of publication. This will be published separately, virtually at cost. The index will include a complete author and subject index from July, 1946, through June, 1951. Preparation of this publication is almost complete and it is scheduled to appear early in 1952. Announcement of publication will be made in *The American Journal of Medicine* and a notice will be sent to all subscribers.

THE EDITOR

Clinical Studies

Clinical and Physiologic Features of Some Types of Pulmonary Diseases with Impairment of Alveolar-capillary Diffusion*

The Syndrome of "Alveolar-capillary Block"

ROBERT AUSTRIAN, M.D., JOHN H. MCCLEMENT, M.D.,† ATTILIO D. RENZETTI, JR., M.D., KENNETH W. DONALD, M.D., RICHARD L. RILEY, M.D. *and* ANDRÉ COURNAND, M.D.

New York, New York

In recent years attempts have been made to isolate patterns of pulmonary dysfunction in a variety of chronic pulmonary diseases.[1] Studies of the physiopathology of the lungs have suggested that alveolar respiratory insufficiency, manifested by arterial oxygen unsaturation and sometimes also by carbon dioxide retention, could result from disturbances of the ventilation-perfusion relationships or from alterations of the pulmonary diffusing surface. The purpose of this paper is to describe a syndrome caused by a variety of pathologic processes and characterized histologically by alterations of the pulmonary diffusing surface, i.e., the alveolar-capillary septa, and physiologically by a reduction in the oxygen diffusing capacity of the lungs. The group of subacute or chronic diseases which leads to this syndrome have common clinical characteristics, prominent among which are the diffuse, finely dispersed pulmonary lesions as revealed by x-ray and those signs and symptoms which result from the physiologic disturbances. The term "alveolar-capillary block" is tentatively offered to identify this syndrome as it describes the essential histologic as well as the principal physiologic features.

The concept that altered permeability of the pulmonary membrane to respiratory gases may cause a reduction in oxygen diffusing capacity is not new. Schjerning[2] in 1922, in attempting to elucidate the early cyanosis of "grippe pneumonia" described by Brauer, suggested that alterations might occur in the lungs without microscopically visible change which could lead to disturbances in the diffusion of oxygen. Between 1932 and 1935 several German authors[3–5] wrote of a syndrome termed by them "pneumonosis" which was believed to arise from decreased permeability of the pulmonary diffusing surface to oxygen and to result from a variety of causes. Among the etiologic agents included were "grippe pneumonia," war gases, chronic pulmonary congestion, amyloid deposits and xanthomatosis. The syndrome was characterized by the development of cyanosis, the cause of which could not be attributed to ventilatory or circulatory disturbances. The complexity of the problem of analyzing the oxygen tension gradient across the pulmonary membrane was appreciated fully, and for lack of sufficiently precise means of analysis the diagnosis of "pneumonosis" remained one of exclusion unless material became available for pathologic examination. In 1944 Hamman and Rich[6] reported four cases of a diffuse pulmonary disease which was characterized clinically by dyspnea, cyanosis and a rapidly advancing course, pathologically by a marked thickening of the alveolar-capillary septa due to deposition of fibrous tissue. The arterial blood oxygen saturation was determined in two of these patients and found to be markedly reduced. However, no other physio-

* From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Cardio-Pulmonary Laboratory of the First Medical and Chest Services (Columbia University Division), Bellevue Hospital, New York, N. Y. The work described in this paper was supported by a grant from the United States Public Health Fund, with additional support from the Commonwealth Fund and the Life Insurance Medical Research Fund.

† James Alexander Miller Research Fellow.

logic studies were carried out to explain this finding.

Elucidation of the problem was carried further by Baldwin, Cournand and Richards[1] who reported on fourteen patients with chronic pulmonary disease not associated with emphysema and characterized by alveolar-respiratory insufficiency. They were grouped under the heading of pulmonary fibrosis, a descriptive pathologic term which subsequent studies have shown to be inapplicable in certain instances. The diseases included in this group were scleroderma of the lung, sulfur dioxide poisoning, exposure to asbestos fibers, lymphangitic carcinomatous metastases to the lungs and pulmonary granulomatosis and fibrosis of unknown etiology. The clinical and physiologic findings in these cases were essentially the same as those demonstrated by the patients to be reported here. From the physiologic data it was inferred that the mechanics of breathing were not altered, that the distribution of gas in the lungs was not abnormal, and that "alveolar-respiratory insufficiency . . . results both from perfusion of large areas of fibrotic tissue which cannot be ventilated and impairment to the adequate diffusion of respiratory gases across a greatly thickened alveolar septa, or reduction in the area of alveolar capillary interface."

Since these earlier reports there has been appreciable progress in the understanding of the oxygen tension gradient existing between alveolar air and systemic arterial blood. The work of Lilienthal, Riley et al.[7] and its subsequent expansion by Riley, Cournand et al.[8–11] have made it possible to assess separately alteration of the pulmonary membrane and abnormal ventilation-perfusion relationships as factors contributing to alveolar-respiratory insufficiency.

Making partial use of the newer technics in a few cases of the pulmonary granulomatosis following exposure to beryllium, Wright and his associates[12] interpreted their observations on alveolar-arterial oxygen tension gradients determined while their patients breathed room air at rest and during exercise as evidence of alterations of the pulmonary diffusing membrane. Bruce and others[13] studying the same type of pulmonary granulomatosis also used some of these newer methods and published figures for oxygen diffusion constants, i.e., oxygen diffusing capacity, which are exceedingly low. However, the significance of the latter data is difficult to assess, not only because the calculated oxygen diffusion constants are inconsistent with the data given for their calculation but also because data obtained while breathing room air cannot be used for such a calculation.

Twelve additional cases which exemplify the essential features, clinical, physiologic and pathologic, of this syndrome of "alveolar-capillary block" are presented here. In these cases all the newer methods for analysis of alveolar-arterial oxygen tension gradient have been employed and in many instances pathologic confirmation of the clinical diagnosis is available. These cases display great variation in the severity and duration of the process, and thus give a fair account of the physiologic basis of the symptoms and signs encountered in the course of this most interesting group of diseases.

METHODS

Measurements of lung volumes, maximum breathing capacity, ventilation and gas exchange during rest, standard exercise and recovery were made according to methods previously described from[1] this laboratory. Arterial blood was obtained through an indwelling needle in the brachial artery. Oxygen content and capacity and carbon dioxide content were determined in the Van Slyke-Neill apparatus. Partial pressures of oxygen and of carbon dioxide in systemic arterial blood were obtained by the direct technic of Riley, Proemmel and Franke,[14] and the carbon dioxide tensions so determined were checked by comparison with values derived by application of blood pH and carbon dioxide content to the line charts of Van Slyke and Sendroy. Sampling of mixed venous blood and determination of cardiac output were carried out by methods previously reported.[15] Measurement of blood pressures in the pulmonary artery, right ventricle and brachial artery were recorded with the use of calibrated Hamilton optical manometers.

Analysis of ventilation-perfusion relationships and of the diffusion characteristics of the lungs was made according to the methods devised by Lilienthal, Riley et al.,[7] and extended by Riley, Cournand and others.[8–10] These methods make possible a quantitative expression, in terms now to be defined briefly, of the effectiveness of ventilation and of perfusion of the lungs and of the permeability of the alveolar-capillary interface.

The Dead Space Ventilation. This represents the portion of the total ventilation which takes

no part in gas exchange. It is made up not only of the actual volume of gas contained in the anatomic dead space but also of a virtual volume of gas arising from the contributions of all alveoli where ventilation is maintained but circulation is reduced or absent. In this manner total ventilation is divided into two components: dead space ventilation and effective alveolar ventilation. The calculation of dead space ventilation is based upon the relationship between alveolar carbon dioxide tension and the carbon dioxide tension of expired air and upon the assumption that arterial and alveolar carbon dioxide tensions are equal.[16] The dead space ventilation is expressed as a percentage of total ventilation and its value in the normal subject does not exceed 30 per cent.

The Venous Admixture in the Arterial Blood. This quantity is made up of an actual volume of mixed venous blood which reaches the peripheral arterial blood by anatomically distinct right to left shunts (bronchial veins, thebesian veins, etc.), and a virtual volume of mixed venous blood, the calculation of which takes into account all the contributions of capillary blood from alveoli in which ventilation is variably reduced in relation to perfusion. This total volume of mixed venous blood is expressed as a percentage of total pulmonary blood flow (cardiac output). Normally this value does not exceed 6 per cent.

The Oxygen Diffusing Capacity of the Lungs. This is a measure of the permeability to oxygen of the alveolar-capillary membrane for the lung as a whole. Diffusion of oxygen across this membrane requires a higher partial pressure of oxygen in the alveolar gas than in the capillary blood. This gradient of oxygen pressure between the alveolus and the capillary is largest at the pulmonary arterial end of the pulmonary capillary, becomes smaller as oxygen is transferred from the alveolus to the capillary and is smallest at the pulmonary venous end of the capillary. By methods that have been described before[10] it is possible to calculate a theoretic mean pressure gradient which, were it present continuously along the alveolar-capillary membrane of the entire lung, would account for the same oxygen transfer that is accomplished by the progressively decreasing alveolar-capillary gradient which actually exists. The oxygen intake per minute divided by this calculated mean pressure gradient is the oxygen diffusing capacity. At rest in normal individuals this value exceeds 15 cc. of oxygen per minute per millimeter of mercury mean pressure gradient.

These last two quantities can be derived from an analysis of the alveolar-arterial oxygen pressure gradient (A-A gradient) at two levels of inspired oxygen concentration. The theoretic considerations upon which this analysis is based, the fundamental assumptions involved and the details of technics and of calculation have been discussed elsewhere.[9,10]

CLINICAL AND PHYSIOLOGIC OBSERVATIONS

Clinical Observations

The vital statistics and diagnoses of the twelve patients are given in Table I. A brief summary of each case history is also given.

Etiology. A variety of diseases have been found to produce the physiologic and clinical pattern reported here. A definite anatomic or etiologic diagnosis could not be made in four of these twelve patients. In the remaining cases the following diagnoses were established by history, biopsy or autopsy: (1) pulmonary granulomatosis after exposure to beryllium in two cases; (2) pulmonary granulomatosis of unknown etiology in one case; (3) Boeck's sarcoid in one case; (4) scleroderma in one case; (5) pulmonary fibrosis of unknown etiology in three cases (in one case after exposure to beryllium; in two cases associated with granulomas in other organs).

Studies on miliary tuberculosis which will be reported elsewhere suggest that during the early and acute phase of this disease a physiologic defect similar to that seen in these cases is present. One patient (Case III) included in this series had a diffuse miliary lesion which cleared completely while streptomycin was being given. Because tubercle bacilli were not found on careful and repeated search, and because significant fever and other toxic manifestations were lacking, a diagnosis of tuberculosis was considered unlikely. However, it is possible that this was a case of chronic or subacute hematogenous pulmonary tuberculosis.

Pathology. Examination of the lungs of some of these patients has shown involvement and thickening of the alveolar-capillary septa to be the predominant pathologic lesion. The alveolar-capillary septa were found to be invaded by fibrous tissue or by the cellular elements of granulomas. Involvement of various parts of the

lung has usually not been uniform, and this inhomogeneity may account for some of the physiologic findings. Some have shown areas of focal emphysema. Involvement of the lymph nodes in those cases with granulomatous diseases has suggested that the pulmonary involvement was only part of a generalized disease.

Laboratory Findings. The usual clinical laboratory observations were seldom abnormal. Polycythemia was seen only twice and was associated with severe right-sided failure in both of these patients.

X-ray. X-ray films of the chest (Figs. 1 to 12) in every case showed involvement of the entire lung field. There was some variation in the size and appearance of the abnormal x-ray shadows which were of the nodular, reticular or conglomerate type. In one case bullae could be identified on the x-ray film. Hilar and mediastinal lymph nodes were enlarged in other cases.

TABLE I

PHYSICAL CHARACTERISTICS AND DIAGNOSIS IN TWELVE CASES WITH "ALVEOLAR-CAPILLARY BLOCK"

Case	Age (yr.)	Sex	Weight (kg.)	Height (cm.)	BSA M^2	Diagnosis	Duration of Illness (mo.)
1. M. B.	34	F	54	161	1.55	Pulmonary granulomatosis (clinical); exposure to beryllium	60
2. M. M.	22	F	47	153	1.42	Scleroderma with pulmonary involvement; (biopsy of skin)	24
3. L. K.	29	M	61	168	1.69	Undiagnosed disease of the lungs	6
4. J. H.	47	F	54	161	1.55	Pulmonary fibrosis of unknown etiology; granuloma of hilar and mediastinal lymph nodes; cor pulmonale; death; (autopsy)	60
5. E. H.	17	M	45	166	1.47	Pulmonary granulomatosis of unknown etiology; (biopsy of lung)	24
6. L. W.	19	F	43	155	1.38	Boeck's sarcoid with pulmonary involvement; (biopsy of lymph node)	60
7. E. L.	47	F	60	167	1.67	Pulmonary fibrosis; Boeck's sarcoid; death; (autopsy)	15
8. F. L.	39	M	70	167	1.79	Pulmonary fibrosis; exposure to beryllium; acute cor pulmonale; terminal bronchopneumonia; death; (autopsy)	24
9. F. S.	43	M	48	165	1.52	Undiagnosed disease of the lungs	42
10. E. M.	60	F	72	151	1.68	Undiagnosed disease of the lungs	11
11. M. H.	64	F	46	150	1.37	Undiagnosed disease of the lungs; cor pulmonale; death; (no autopsy)	84
12. J. Hi.	66	M	55	169	1.63	Pulmonary granulomatosis; exposure to beryllium; spontaneous pneumothorax; death; (autopsy)	Several years?

Symptomatology. In most of the patients the disease was insidious in onset and marked by increasing dyspnea on exertion and later at rest. Cough was present in all instances and was productive usually of small amounts of tenacious mucoid sputum. Significant weight loss occurred in many instances. In the recent history it was not unusual to find febrile episodes with pulmonary symptoms.

Physical Examinations. The striking physical findings included tachypnea at rest, limited excursion of the thorax, the presence of persistent fine rales heard usually over the lower lobes, and accentuation of the second pulmonic heart sound. Cyanosis significantly was absent or of minimal degree at rest, except in the terminal stages of the disease, but appeared rapidly on mild exertion. Clubbing of the fingers was noted occasionally.

Clinical Course. These twelve patients illustrated all possible courses from complete clinical recovery to fatal outcome. Thus in one instance (Case III), under the influence of antibiotic therapy (streptomycin), x-ray and clinical regression took place and has been maintained over a one-and-a-half year period. In another patient (Case II) who was observed and studied during a one and one-half-year period there were no changes in the clinical manifestations of this syndrome. However, the most common course seems to be a steady progression in the symptoms of pulmonary insufficiency, with in-

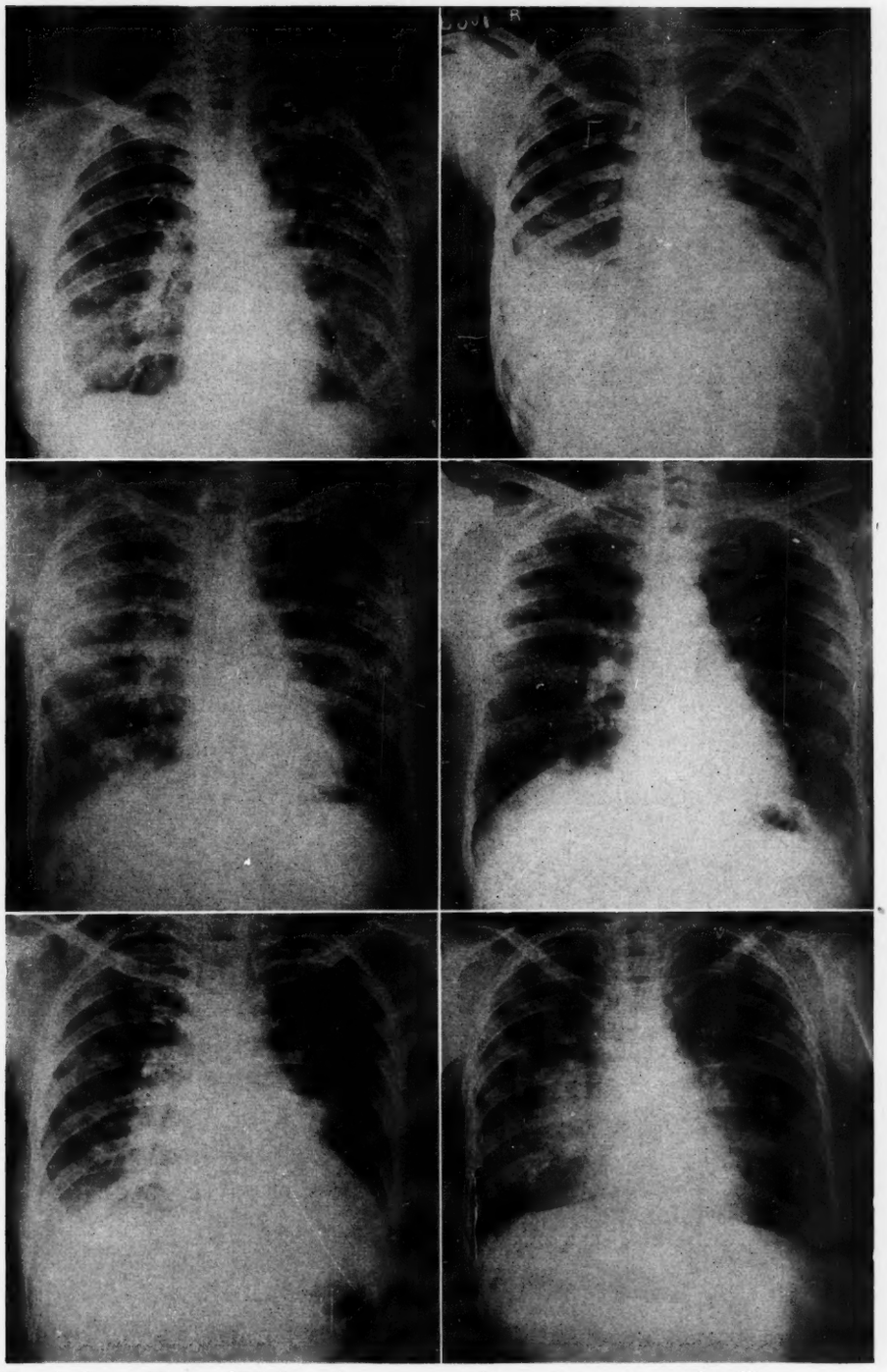

FIG. 1. Case I. X-ray of M. B.; pulmonary granulomatosis; exposure to beryllium.
FIG. 2. Case II. X-ray of M. M.; scleroderma with pulmonary involvement.
FIG. 3. Case III. A, x-ray of L. K.; undiagnosed disease of lungs before streptomycin therapy; B, x-ray after streptomycin therapy.
FIG. 4. Case IV. X-ray of J. H.; pulmonary fibrosis of unknown etiology.
Fig. 5. Case V. X-ray of E. H.; pulmonary granulomatosis of unknown etiology.

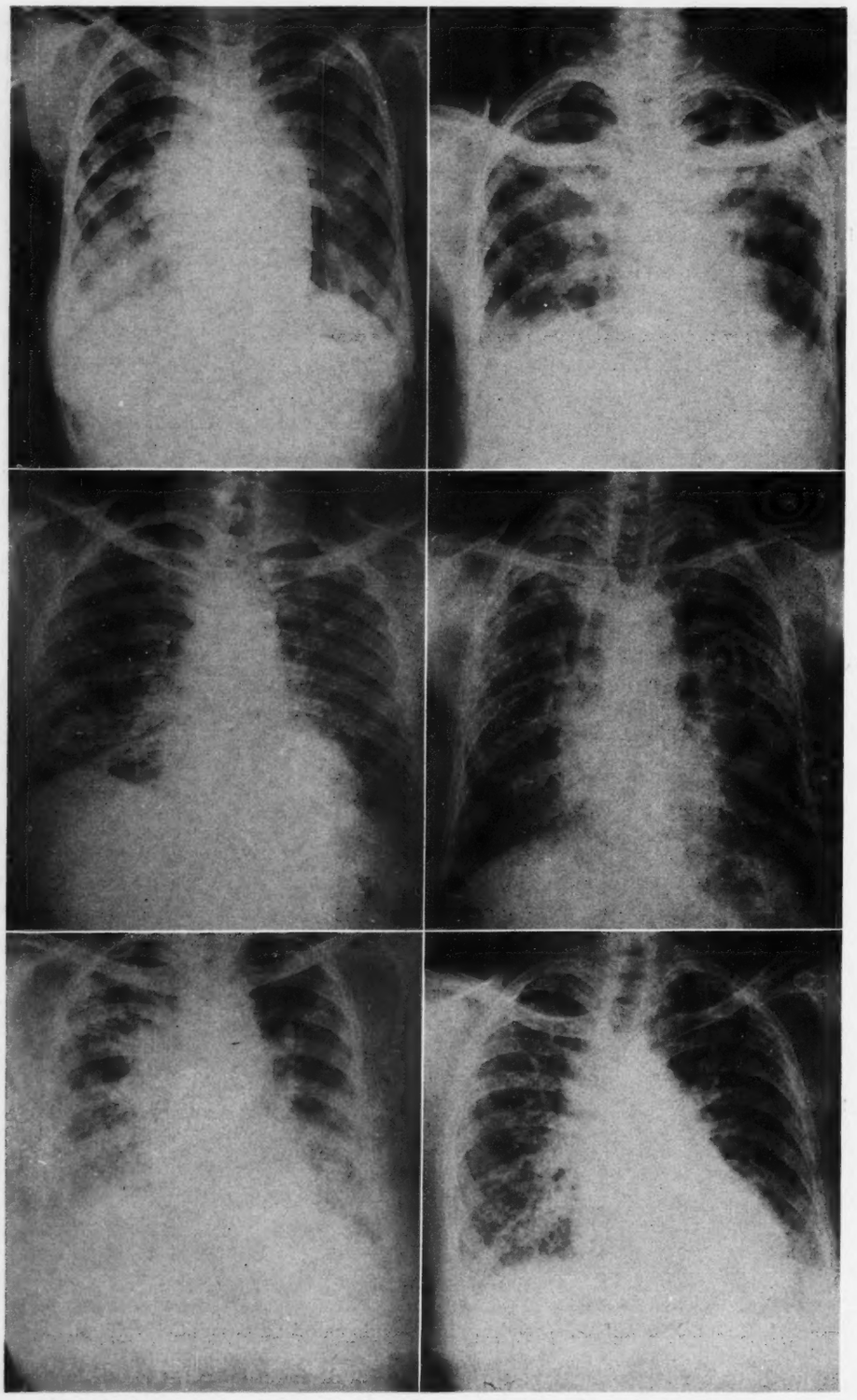

Fig. 6. Case VI. X-ray of L. W.; Boeck's sarcoid with pulmonary involvement.
Fig. 7. Case VII. X-ray of E. L.; pulmonary fibrosis; Boeck's sarcoid.
Fig. 8. Case VIII. X-ray of F. L.; pulmonary fibrosis; exposure to beryllium.
Fig. 9. Case IX. X-ray of F. S.; undiagnosed disease of the lungs.
Fig. 10. Case X. X-ray of E. M.; undiagnosed disease of the lungs.
Fig. 11. Case XI. X-ray of M. H.; undiagnosed disease of the lungs.

creasing dyspnea, cyanosis and inability to exercise. The rate at which these symptoms progress is quite variable, and the interval from the first appearance of symptoms to profound pulmonary insufficiency has varied from a few months to several years. In some of the cases the appearance of irreversible right heart failure has modified the course and hastened a fatal outcome. Acute respiratory infections occurred in some and were controlled by antibiotics. The course of one patient (Case XII) was complicated by the development of a spontaneous pneumothorax.

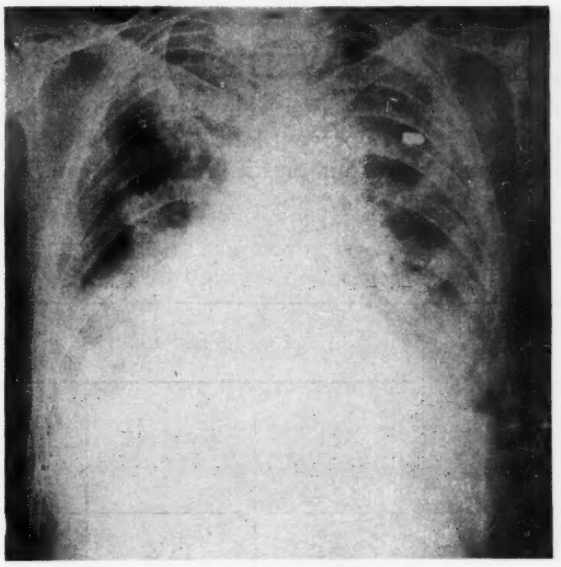

FIG. 12. Case XII. X-ray of J. H.; pulmonary granulomatosis; exposure to beryllium.

Physiologic Observations

The physiologic data are recorded in Tables II to VI. The characteristic findings were as follows: Measurements of the *lung volumes* demonstrated a significant reduction in the total pulmonary capacity which in general was associated with a parallel reduction in each of its subdivisions. As a result, the ratio of residual volume to total capacity remained normal in all but three instances, and in these the low concentration of alveolar nitrogen after the patient had breathed 99 per cent oxygen for seven minutes and the appearance of the spirograms indicated that no obstructive emphysema was present.

The *maximum breathing capacity* was close to normal in almost all cases and in fact was greater than the predicted value in seven of the twelve.

TABLE II

LUNG VOLUMES AND MAXIMUM BREATHING CAPACITY IN TWELVE CASES WITH "ALVEOLAR-CAPILLARY BLOCK"

Case	Vital Capacity % Predicted	Residual Volume % Predicted	Total Lung Capacity % Predicted	$\frac{\text{Residual Volume}}{\text{Total L. Capacity}} \times 100$	Maximum Breathing Capacity % Predicted
Normal	100	100	100	<35	100
1. M. B.	73	70	75	19	116
2*a*. M. M.	33	47	37	33	86
b. M. M.*	25	43	32	35	75
3*a*. L. K.	63	115	73	25	120
b. L. K.*	85	90	86	21	127
4*a*. J. H.	42	43	42	26	107
b. J. H.*	36	30	38	20	109
5. E. H.	51	84	58	28	89
6. L. W.	32†	63	38†	44†	67
7. E. L.	37	44	36	32	82
8*a*. F. L.	51	64	57	28	106
b. F. L.*	49	36	45	20	95
9. F. S.	51	56	51	27	108
10. E. M.	42	100	52	46	94
11. M. H.	26	72	42	44	76
12. J. Hi.	50	70	58	29	108

* Refers to a second study; M. M. = 18 months later, no change in clinical status; L. K. = 2½ months later, after streptomycin treatment; J. H. = 18 months later, after development of congestive heart failure; F. L. = 1½ months later, after treatment with cortisone, 12 days before death.

† Poor cooperation was obtained in determining the vital capacity.

The presence of constant and at times extreme hyperventilation was demonstrated by studies during rest, standard exercise and recovery. In spite of a large maximum breathing capacity this hyperventilation resulted in an abnormal reduction of the breathing reserve, especially during exercise and recovery from exercise in all but three patients.

The *arterial oxygen saturation* fell from a normal or minimally reduced value at rest to a distinctly low value during exercise. In every instance the calculated *alveolar oxygen tension* was normal, and in several of the cases exceeded the normal level. The *alveolar-arterial oxygen tension gradient* was increased above normal in all patients when breathing room air at rest but in three of the cases this increase was small and probably insignificant. Of greater importance is the fact that all members of this group had an abnormally large alveolar-arterial oxygen tension gradient when breathing an atmosphere with an oxygen concentration lower than that of ambient air. In most instances the alveolar-arterial oxygen gradients measured at two levels of inspired oxygen concentration were of nearly equal magnitude. The *oxygen diffusing capacity* was found to be lower than normal under resting conditions in the eleven patients in whom it was measured.

Analysis of *ventilation-perfusion relationships* revealed a significant increase in the degree of calculated *venous admixture* in nine of the eleven cases in whom it was determined. It should be noted, however, that cardiac output was of sufficient magnitude to supply a normal effective pulmonary blood flow, measured in absolute terms, despite the increased fraction of venous admixture.

An increase in *physiologic dead space* was noted in most of the cases. By constant and often marked hyperventilation, normal or increased values for effective alveolar ventilation were maintained even in those cases with a very large physiologic dead space.

Studies of the *hemodynamics* of the pulmonary circulation revealed a mild to marked degree of hypertension in the pulmonary artery in all patients in whom measurements were made during a steady state of mild exercise. The cardiac output at rest was normal or increased

TABLE III

VENTILATION AND BREATHING RESERVE DURING THE STANDARD EXERCISE TEST AND INDEX OF INTRAPULMONARY MIXING IN TWELVE CASES WITH "ALVEOLAR-CAPILLARY BLOCK"

Case	Ventilation			Breathing Reserve		Index of Intrapulmonary Mixing N_2 %
	Rest (L./min./M²)	Exercise† (L./min./M²)	1st Minute Recovery (L./min./M²)	Exercise† (L./min.)	1st Minute Recovery (L./min.)	
Normal	3.4	10.6	12.4	72	70	2.50
1. M. B.	4.3	17.4	22.6	90	73	1.03
2*a*. M. M.	5.1	16.1	14.4	51	54	1.01
b. M. M.*	6.1	15.5	18.7	43	24	0.90
3*a*. L. K.	6.2	25.1	21.7	102	100	1.39
b. L. K.*	3.8	26.2	12.5	100	133	1.41
4*a*. J. H.	5.0	14.7	22.7	59	43	1.29
b. J. H.*	7.8	....	....	...	...	0.87
5. E. H.	7.8	24.5	23.2	66	60	1.00
6. L. W.	7.1	14.7	13.0	37	28	0.96
7. E. L.	7.9	26.9	15.8	21	36	1.43
8*a*. F. L.	5.9	13.8	16.5	100	96	1.04
b. F. L.*	6.0	18.7	23.1	82	66	1.68
9. F. S.	9.0	30.7	29.5	58	63	1.05
10. E. M.	5.4	17.0	18.1	39	26	1.23
11. M. M.	10.1	....	....	...	...	0.97
12. J. Hi.	9.1	....	....	...	...	2.58

* Second study as in Table II.

† Standard exercise = Stepping up and down a platform 20 cm. high thirty times in one minute.

in all cases without congestive failure and was significantly decreased in two cases when it was measured during cardiac decompensation. The increase in cardiac output during mild exercise was in the expected range.

series. Increasing disability from this syndrome does seem to be related to the appearance of arterial oxygen unsaturation at rest, and in the final stages to a return of the usually low arterial carbon dioxide tension at rest to normal or

TABLE IV

MEASUREMENTS OF GAS EXCHANGE IN TWELVE CASES WITH "ALVEOLAR-CAPILLARY BLOCK"

Case	Oxygen Consumption		Oxygen Consumption per L. Ventilation		Arterial Blood			
						Oxygen Saturation		
	Rest cc./min./M²	Exercise* cc./min./M²	Rest cc./L.	Exercise* cc./L.	Oxygen Capacity cc./L.	Rest %	1st Min. Recovery %	pCO_2 Rest mm. Hg
Normal	132	494	45.1	55.8	190	98	98	39
1. M. B.	138	486	39.4	34.4	182	98	84	37
2*a*. M. M.	138	349	25.3	25.8	158	96	79	37
b. M. M.†	114	389	29.0	30.2	118	93	80	38
3*a*. L. K.	190	604	37.5	34.8	213	96	88	31
b. L. K.†	136	682	43.7	50.5	206	98	96	35
4*a*. J. H.	121	333	29.3	27.0	146	96	79	37
b. J. H.†	138	...	20.9	....	199	90	..	33
5. E. H.	186	485	29.0	24.1	189	92	86	38
6. L. W.	153	367	25.9	30.0	185	96	74	40
7. E. L.	151	592	27.9	26.3	171	94	81	34
8*a*. F. L.	133	331	27.5	29.3	200	96	75	33
b. F. L.†	139	421	28.6	27.3	201	90	68	33
9. F. S.	151	373	18.8	14.7	181	91	72	43
10. E. M.	130	358	28.5	20.5	186	92	67	39
11. M. H.	144	...	17.0	....	198	78	..	43
12. J. Hi.	158	...	21.6	....	170	89	..	42

* See footnote Table III.

† Second study as in Table II.

Observations on the physiologic course of this syndrome are available not only from studies on several patients at different clinical stages of their disease but also from repeated studies of the same patients.

In the tables and case histories the patients have been arranged in order of increasing severity of their disability, as judged from their clinical findings when first seen. This arrangement makes it apparent that the disability is neither related to the reduction of lung volume nor to the maximum breathing capacity. The residual volume/total capacity ratio was increased in some of the patients with the most severe disease. An increase in this ratio has been reported by others[12] in some cases of pulmonary granulomatosis following exposure to beryllium but it was not observed in such patients in this slightly increased levels. The more advanced cases have in general a large physiologic dead space and venous admixture, and there appears to be some relationship between the severity of the disease and the degree of reduction of the oxygen diffusing capacity.

Four of the twelve cases were studied twice. In one patient with generalized scleroderma (Case II) there was no significant change during an eighteen-month period. During a similar interval in another patient (Case IV) with a granulomatous disease of the lungs there was marked physiologic change with the appearance of arterial oxygen unsaturation at rest, an increase in the A-A pO_2 gradients at rest both while breathing room air and a low oxygen mixture, a further decrease in the oxygen diffusing capacity, and an increase in the venous ad-

mixture and the dead space. In the latter patient irreversible congestive failure had developed, and a reduction in the cardiac output was observed a short time before death. More rapid progression took place in one of the patients (Case VIII) who had been exposed to beryllium phosphors. During a period of 1½ months it was observed that arterial oxygen unsaturation at rest appeared and that there had been a marked increase in the alveolar-arterial oxygen tension gradient both while breathing room air and a lower inspired oxygen concentration.

The physiologic changes which accompany clinical improvement in this syndrome were observed only once (Case III) in the patients reported here. This improvement occurred, as has been previously mentioned, during treatment with streptomycin and was characterized by a slight increase in lung volume; a marked decrease in hyperventilation at rest and during the first minute of recovery from exercise, a decrease in the resting oxygen consumption, the presence of a normal arterial oxygen saturation after exercise and a return to normal of the oxygen diffusing capacity of the lungs and the percentage of venous admixture. However, it is of interest that there was no change in the degree of pulmonary hypertension after exercise.

TABLE V

MEASUREMENT OF VENTILATION-PERFUSION RELATIONSHIP AND OXYGEN DIFFUSING CAPACITY IN TWELVE CASES WITH "ALVEOLAR-CAPILLARY BLOCK"

Case	Dead Space Ventilation in % Total Ventilation	Effective Alveolar Ventilation (L./min./M²)	Alveolar pO_2 Room Air (mm. Hg)	A-A Gradient at Two Levels of Oxygen		Oxygen Diffusing Capacity of the Lung (D_{LO_2})	Venous Admixture in % of Cardiac Output
				Room Air	Low O_2		
Normal	30	2.2	100	12	12	15	6
1. M. B.	27	3.1	114	27	26	10	13
2*a*. M. M.	26	3.8	109	13	33	5	3
b. M. M.*	33	3.2	105	19	23	5	5
3*a*. L. K.	26	4.6	121	30	32	10	12
b. L. K.*	15	3.2	116	16	12	17	5
4*a*. J. H.	38	3.1	120	23	22	9	8
b. J. H.*	46	4.2	112	44	27	6	14
5. E. H.	42	4.5	110	34	30	8	14
6. L. W.	44	4.0	111	34	29	7	13
7. E. L.	46	4.3	114	33	31	7	15
8*a*. F. L.	46	3.2	102	16	22	7	6
b. F. L.*	33	4.0	114	45	43	..	..
9. F. S.	67	3.0	107	53	42	6	34
10. E. M.	40	3.2	98	16	32	..	..
11. M. H.	57	4.4	98	61†	49	4	25
12. J. Hi.	58	3.8	106	46	43	6	22

* Second study as in Table II.

† Inspired oxygen concentration 25 per cent.

COMMENTS

From these observations it is possible to identify a syndrome, "alveolar-capillary block," which has distinct clinical, pathologic and physiologic features. Most of the findings characteristic of this condition were described previously by Baldwin, Cournand and Richards.[1] The clinical observations made here extend the list of pathologic processes with which the syndrome is associated to include Boeck's sarcoid and the granulomatosis following exposure to beryllium. In the earlier work five cases of Boeck's sarcoid were reported but in all of these cases the only physiologic abnormalities found were characteristic of isolated ventilatory insufficiency and no evidence of interference with the transfer of oxygen to the arterial blood was discovered. The present study makes it clear, however, that in some cases of Boeck's sarcoid with pulmonary involvement there may be an impedance to the diffusion of oxygen. The

reason for these different physiologic patterns is not clear.

It is possible that the lesions in some cases are located predominantly in the alveolar-capillary septa while in others they are chiefly elsewhere. It may also be that although involvement of this region is always present it is neither severe enough nor sufficiently widespread to interfere with diffusion in the lung as a whole; or the granulomatous lesions are such that they produce an obliteration of both alveolus and capillary, a condition which would produce impedance to diffusion only if it was very extensive. The finding of another case of pulmonary granulomatosis, in which the granulomas contained numerous foreign body giant cells and bi-refractile crystals confirms the earlier observation[1] that a granulomatous lesion of as yet unknown etiology but, with these particular histologic characteristics, may be among the causes of this syndrome. The inclusion of the beryllium cases in this group confirms the assumption of Wright and others[12] that there is an interference with the diffusion of oxygen across the alveolar membrane in such patients. With the physiologic data available in the work of Baldwin and her associates referred to, the reasons for the defective gas exchange could not be precisely defined. Although the results of this study lend strong support to the previous inferences that this syndrome is characterized primarily by a disturbance in the diffusion of oxygen across the alveolar membrane, the new information has also revealed that the distinction between diffusion defects and disturbances in the ventilation-perfusion relationships is not absolutely clear-cut in the late or advanced stages of these diseases. Finally, hemodynamic measurements in all patients and complete studies on two different occasions in four patients have served to give a more comprehensive description of this syndrome.

Analysis of the results of physiologic studies yields information about the derangement of

TABLE VI

HEMODYNAMIC MEASUREMENTS IN TWELVE CASES WITH "ALVEOLAR-CAPILLARY BLOCK"

Case	Pulse Rate	Oxygen Consumption (cc./min./M²)	Arterio-Venous Oxygen Difference (cc./L.)	Cardiac Index (L./min./M²)	Pulmonary Artery		Systemic Artery	
					s/d (mm. Hg)	m (mm. Hg)	s/d (mm. Hg)	m (mm. Hg)
Normal								
Rest	...	126	39	3.3	20/9	13	112/65	84
Exercise	...	(406)*	(73)	(5.4)	(13/4)	(11)	(125/78)	(100)
1. M. B.	84	133	34	3.9	21/9	15	130/78	103
	(120)	(301)	(59)	(5.1)	(26/9)	(18)	(174/100)	(139)
2*a*. M. M.	79	133	37	3.6	32/13	20	95/57	74
	(105)	(313)	(60)	(5.2)	.....	(39)	(140/85)	(104)
b. M. M.†	70	141	38	3.7	29/12	19	134/87	106
3*a*. L. K.	100	185	38	4.9	30/12	19	126/75	93
	(120)	(317)	(49)	(6.5)	(46/13)	(24)	(124/61)	(83)
b. L. K.†	82	174	46	3.8	28/12	18	145/94	114
	(104)	(376)	(59)	(6.4)	(38/15)	(24)	(156/102)	(122)
4*a*. J. H.	96	115	31	3.7	35/14	23	123/83	100
b. J. H.†	115	196	73	2.7	.....	..	.....	...
5. E. H.	107	196	41	4.8	35/14	23	96/63	75
6. L. W.	110	165	46	3.6	34/15	24	.....	...
7. E. L.	82	149	44	3.4	24/12	17	112/69	84
	(92)	(280)	(56)	(5.0)	(44/21)	(31)	.....	...
8*a*. F. L.	80	140	49	2.9	30/14	21	108/80	92
9. F. S.	115	159	45	3.5	27/10	17	.....	71
10. E. M.	90	126	39	3.2	58/20	34	121/69	91
11. M. H.	92	144	56	2.6	69/25	43	120/59	81
12. J. Hi.	80	164	34	4.8	.....	..	125/62	87

* Figures in parentheses represent exercise data obtained during "steady state" exercise.
† Second study as in Table II.

cardiopulmonary function. Reduction of the total pulmonary capacity is not remarkable when one considers the extensive fibrotic or granulomatous involvement of the lungs. The pathologic process apparently reduces the available air spaces. The normal or nearly normal ratio of residual volume to total capacity in all but three instances, together with the normal spirograms, suggests that generalized emphysema is not a part of this pattern; in fact, when pathologic examination demonstrates any emphysema, it is usually of the focal type.

The persistence of a normal maximum breathing capacity with such widespread pulmonary disease is of interest. It implies that the relationship which exists normally between the motive forces produced by the chest muscles to deform the lung and those resulting from the elastic and non-elastic resistances in the lung has not been greatly modified even under conditions of maximum effort. If the anatomic changes in these lungs tend to increase their elastic resistance, as seems likely, and if continuous hyperventilation is present, as it is, hypertrophy of the respiratory muscles or improvement in their coordination must have taken place to account for this well preserved maximum breathing capacity.

Various mechanisms may be involved in the marked hyperventilation at rest and during exercise. In characterizing this syndrome emphasis has been placed on the lack of arterial anoxia at rest in all but the most abnormal cases. Thus anoxia cannot be implicated in the resting hyperventilation and it must be due either to some abnormal reflex stimulus to the respiratory center or to a respiratory center in which chemosensitive cells are more than normally sensitive to carbon dioxide (supranormal centrogenic drive). The infiltrative process in the lungs may well give rise to excessive stimuli via the stretch reflexes and thus explain the initiation of hyperventilation. Once established, hyperventilation leads to lowering of arterial carbon dioxide tension which in turn is followed by a reduction of the alkaline reserve. Both of these have been observed in many of the patients reported here. As has been shown in altitude studies,[17] the existence of a decreased alkaline reserve lowers the threshold of stimulation of the respiratory center to carbon dioxide. Thus a supranormal centrogenic drive may be present and may well act as an additional factor in maintaining hyperventilation. The marked arterial oxygen unsaturation which occurs during exercise will produce, by its effect on the chemosensitive cells of the carotid body, an additional strong stimulus to ventilation.

The impairment of oxygen transfer from the atmosphere to the blood constitutes the most interesting and important defect observed in this syndrome. The consistently high alveolar oxygen tensions which are present eliminate the possibility of any defect in the transfer of oxygen from atmosphere to alveolus. Of the two causes for the increased oxygen gradient between the alveolus and the arterial blood, namely, abnormal ventilation-perfusion relationships and a reduced oxygen diffusing capacity, the latter is of much greater significance in this syndrome. In contrast to the sometimes normal physiologic dead space and percentage of venous admixture all of these individuals had a reduction in the oxygen diffusing capacity of the lung. The low diffusing capacity may either be due to a reduction in the total area of alveolar membrane which is available for the diffusion of gases, or to a reduction in the permeability of this membrane per unit of area, or to both. The observation of rather widespread thickening of the alveolar capillary septa suggests that the reduction in permeability per unit area is the major reason for the low diffusing capacity. Whether the area of alveolocapillary interface is also reduced under resting conditions cannot be determined.

The observation that many of these patients have a normal resting arterial oxygen saturation while breathing room air at rest is not surprising, even in the presence of a significant reduction of the resting oxygen diffusing capacity. The theoretic considerations developed by Riley and others[9] indicate that in spite of a marked reduction of the oxygen diffusing capacity, the pulmonary capillary blood will still be almost fully saturated if the alveolar oxygen tension is normal. The marked arterial oxygen unsaturation that occurs in these patients after exercise is probably related to a reduced ability to increase the oxygen diffusing capacity of their lungs. Lilienthal, Riley et al.[7] have shown that the increase in oxygen intake that occurs during severe exercise in normal subjects is associated with a six- to seven-fold increase in their oxygen diffusing capacity. It would seem reasonable to assume that this larger O_2 diffusing capacity results from an increase in the area available for gaseous diffusion. The finding of an increase in the pulmonary artery pressure during mild

exercise in all cases in which it was measured suggests that these patients may be unable to increase the area of their pulmonary capillary bed during exercise. Hence such an inability to increase area would prevent the increase in oxygen diffusing capacity necessary to maintain a normal arterial oxygen saturation.

The dead space and venous admixture measurements were abnormal in some of these patients. Such abnormalities usually indicate defective ventilation-perfusion relationships; yet, by other tests these individuals had efficient intrapulmonary gas mixing and alveolar ventilation and no emphysema. Riley et al.[9] point out that by the analysis employed here the only method of distinguishing between distribution and diffusion effects is based on the assumption that alveolar and capillary carbon dioxide tensions are identical at the end of the capillary. They further state that "a small but significant carbon dioxide diffusion gradient exists in . . . cases in which diffusion is severely impaired in all parts of the lungs, but more severely impaired in some parts than others." In such instances the presence of this gradient contributes to the measurements of dead space and venous admixture.

The distinctive characteristics of the pulmonary circulation in this syndrome have been previously discussed briefly.[18] In those patients without cardiac failure an increase in cardiac output was often observed and was associated with a higher than normal oxygen intake. The consistency of these two findings in this group of patients does not seem to be due to the absence of a "steady state" or to the presence of anxiety. These patients appeared as free of anxiety as other patients with different diagnoses who were studied during the same period and who did not show larger than normal oxygen intake. Furthermore, on repeated measurements, with or without a cardiac catheter in place, the oxygen intake was elevated. It is likely therefore that the disseminated and active pathologic process found in many of these cases caused an increased metabolism. When right heart failure developed in the final stages of two of these patients, the low cardiac output was in distinct contrast to what has been described in cases of chronic pulmonary emphysema with anoxia, but similar to what is observed in cases of pulmonary disease with restriction of the pulmonary vascular bed. The elevated pulmonary artery pressure which was noted in nearly every case must be due to a reduced vascular bed since anoxia is present only during exercise until late in the course of this syndrome. Finally, it must be emphasized that the absence of a continuous anoxic stimulus to the bone marrow probably explains the absence of polycythemia in most of these patients. It was only in the terminal stages, when arterial anoxia of severe degree develops at rest, that a significant increase in red blood cell volume was observed.

CASE REPORTS

CASE I. M. B., a thirty-four year old white female was admitted to the hospital on February 8, 1949, complaining of shortness of breath of four to five years' duration. Between the ages of eighteen and twenty-two years she was exposed to beryllium phosphors while working in a factory which made fluorescent light bulbs. At about the age of thirty the patient became aware of mild exertional dyspnea and fatigability. A year later a routine x-ray film of her chest was abnormal. Her exertional dyspnea continued but did not progress.

The only significant physical findings were moderate tachypnea, an accentuated second pulmonic sound and slight clubbing of the fingers. There was no cyanosis. X-ray of the chest showed fine nodular infiltration distributed evenly throughout both lung fields. (Fig. 1.)

There was no change in her status while she was in the hospital and she was discharged to her home.

CASE II. M. M. was a twenty-two year old colored woman. Two years before hospitalization depigmentation in the left scapular region occurred. A year later changes characteristic of scleroderma were noted in the skin of the face and upper extremities. At this time the patient developed a cough and mild dyspnea on exertion. She was admitted to the hospital on May 24, 1948, and presented the physical findings of well established scleroderma. In addition, thoracic expansion was limited, fine rales were heard posteriorly over both lungs and the second pulmonic sound was accentuated. There was no tachypnea nor clubbing of the fingers.

X-ray of the chest (Fig. 2) showed diffuse fine nodular infiltrates in both lungs. Barium swallow demonstrated delayed emptying of the esophagus.

She was readmitted to the hospital for physiologic studies eighteen months after her first admission. During this interval there had been

no change in her clinical findings. The effect of treatment with cortisone in this patient has been reported elsewhere.[20]

CASE III. L. K. was a twenty-nine year old white Polish man admitted to the hospital on September 20, 1948, complaining of weakness, shortness of breath on exertion and night sweats of four months' duration. Six years prior to admission he had bilateral pneumonia complicated by pleural effusion and pericarditis from which he had recovered. His present illness began insidiously with the development of vague thoracic discomfort, fatigability and occasional elevations of temperature to 99°F. An x-ray of the chest taken four months after the onset of symptoms demonstrated bilateral fine nodular infiltration of the lungs.

Physical examination revealed a well developed, thin patient who did not appear seriously ill. He showed mild tachypnea, slight limitation of chest expansion and fine rales over the lower half of each lung posteriorly. The tuberculin reaction was positive. Tubercle bacilli were never recovered from his sputum. An electrocardiogram shortly after admission showed a prolonged P-R interval. X-ray of the chest showed fine nodular shadows scattered throughout both lung fields. (Fig. 3A.)

The patient was treated with streptomycin, receiving 1 gm. daily for forty-two days. Coincident with therapy the respiratory symptoms decreased, his slightly productive cough disappeared and he gained 18 pounds. These clinical findings were associated with marked clearing of the pulmonary infiltration (Fig. 3B) and with a return of the electrocardiogram to normal. The patient was discharged and has remained well for eighteen months.

CASE IV. J. H., a forty-seven year old colored female, had had four respiratory illnesses in the eight years preceding her first admission, on March 21, 1949. Each was characterized by fever, cough productive of small amounts of mucoid sputum and weight loss. Her chest x-ray was known to have been abnormal for at least four years before her first admission, and dyspnea on exertion had been present for about two years. On physical examination she appeared chronically ill. There was tachypnea, moderate axillary lymph node enlargement, limited chest expansion, rales at the base of both lungs, a greatly accentuated second pulmonic sound and clubbing of the fingers.

X-ray of the chest (Fig. 4) revealed irregular and coarse infiltration of both lungs. The electrocardiogram was normal. Hematocrit was 39 and blood volume was normal.

Sections of an axillary lymph node showed replacement of lymphoid tissue by numerous discrete and confluent epitheloid tubercles containing large numbers of foreign body type giant cells. Within the giant cells were noted large fragments of doubly refractile crystalline material.

The patient had another admission one and a half years later because of the abrupt onset of fever and an increase in her cough and dyspnea. On physical examination she was acutely ill. Her temperature was 104°F., pulse 120 and respirations 60 per minute. Cyanosis, severe dyspnea, ankle edema and enlargement of the liver were now present in addition to her previous findings. The x-ray of the chest showed no significant change from that of her previous admission but the electrocardiogram now showed evidence of right ventricular hypertrophy.[19]

The white blood count was 14,250, venous pressure 190 mm. saline, decholin circulation time 25 seconds and hematocrit 47 per cent. She was given penicillin, aureomycin, digitalis and mercurial diuretics with a dramatic temporary improvement in her dyspnea and a rapid fall in her temperature. For a brief period after admission her edema cleared, but her dyspnea remained severe enough to confine her to bed. During the four months that she remained in the hospital on this second admission there was a steady increase in her dyspnea, cyanosis and signs of right-sided cardiac failure. For a brief period she also received cortisone, without definite benefit. Progressive cardiorespiratory insufficiency resulted in death.

Autopsy showed widespread pulmonary fibrosis (Fig. 13) involving the alveolar-capillary septa. There was evidence of bronchiectasis at both bases. No granulomatous lesions were found in the lungs but granulomatous lesions containing epithelioid cells, foreign body giant cells and bi-refractile crystals were present in the hilar and mediastinal lymph nodes. These lesions were similar to those found in Case v. Marked right ventricular hypertrophy was present.

CASE V. E. H., a seventeen year old white boy was admitted to the hospital on November 11, 1949, with the chief complaint of weakness. Two years previously he had had "virus pneumonia" marked by a prolonged convalescence. Thereafter the patient was never free of cough.

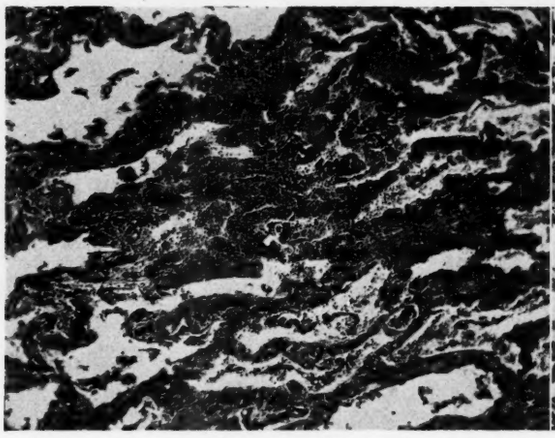

FIG. 13. Case IV. Microscopic section of lung of J. H.; pulmonary fibrosis of unknown etiology; hematoxylin and eosin stain; × 160.

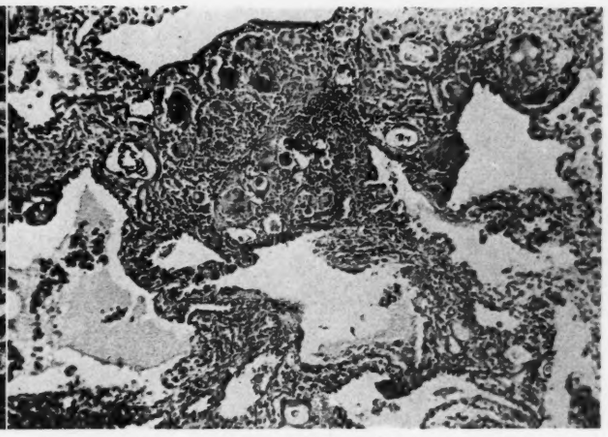

FIG. 14. Case V. Biopsy of lung of E. H.; pulmonary granulomatosis of unknown etiology; hematoxylin and eosin stain; × 160.

For a year he had noted increasing exertional dyspnea. Two weeks before admission he had an increase in dyspnea, intermittent pleuritic pain in the left chest, anorexia and low-grade fever. On physical examination the patient appeared poorly nourished. There was tachypnea, fine rales at the lung base, slightly enlarged supraclavicular and axillary lymph nodes and clubbing of the fingers.

X-ray of the chest (Fig. 5) showed a bilateral diffuse granular infiltration. There was also bilateral hilar and mediastinal lymph node enlargement. Biopsies of the lung (Fig. 14), mediastinal and axillary lymph nodes were obtained. The lung biopsy revealed disruption of pulmonary architecture by granulomas in the peribronchial and perivascular connective tissue and in the interalveolar septa. The lesions were discrete, consisting of epithelioid and giant cells of the foreign body type, the latter containing laminated, crystalline, doubly refractile bodies. Mediastinal and axillary lymph nodes showed almost complete replacement of the normal gland structure by similar granulomas. The effect of treatment with cortisone upon the clinical, physiologic and pathologic picture in the patient has been reported separately.[20]

CASE VI. L. W., a nineteen year old colored woman, was admitted to the hospital on September 11, 1950. About five years before admission she became aware of shortness of breath on exertion which slowly but steadily progressed in severity. At that time she also noted the appearance of nodular swellings on her nose. For about two years preceding admission she had a cough productive of small amounts of whitish sputum and a progressive weight loss which amounted to 17 pounds. On physical examination she appeared chronically ill. There were several discrete, non-ulcerated nodules about the tip of the nose. The lungs were normal. There was an accentuated second pulmonic sound.

X-ray of the chest (Fig. 6) showed a broadened mediastinum and finely nodular densities, closely packed, scattered through both lung fields. X-ray of the hands showed multiple cystic changes in the phalanges. Two cultures and four smears of her sputa failed to show tubercle bacilli. Her skin test to old tuberculin was positive. The albumin/globulin ratio was 4.2/5.0. Biopsies of one of the skin nodules and of a cervical lymph node showed a granulomatous lesion consistent with the diagnosis of Boeck's sarcoid. The electrocardiogram showed evidence of right ventricular hypertrophy.[19]

The effect of treatment with cortisone upon the clinical and physiologic picture in the patient is to be reported at a later date.

CASE VII. E. L., a forty-seven year old colored woman, was admitted to the hospital on December 4, 1948, complaining of cough and weight loss. In the past she had worked as a dispenser of cosmetics. In the year prior to admission she gradually developed a respiratory illness characterized by cough which was at first non-productive, increasing dyspnea and orthopnea and a weight loss of 30 pounds. Six months before admission a chest x-ray was found to be abnormal.

Physical examination revealed a well developed, somewhat undernourished woman who appeared both acutely and chronically ill.

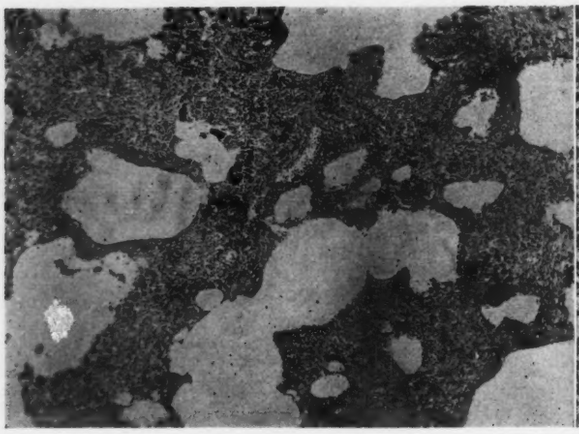

FIG. 15. Case VII. Microscopic section of lung of E. L.; pulmonary fibrosis; hematoxylin and eosin stain; × 160.

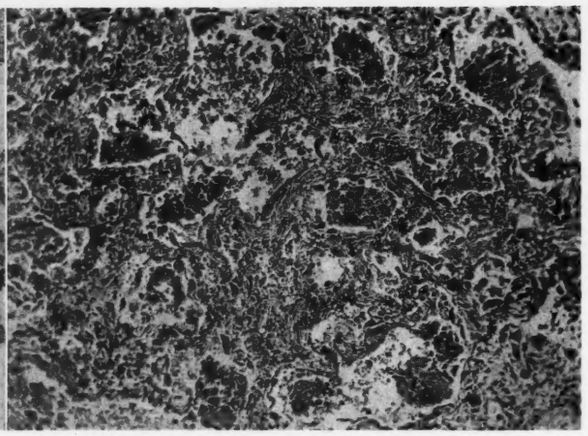

FIG. 16. Case VIII. Microscopic section of lung of F. L.; pulmonary fibrosis; exposure to beryllium; hematoxylin and eosin stain; × 160.

Respirations were rapid and panting in character and bouts of dyspnea were occasioned by paroxysms of cough productive of scant amounts of mucoid, slightly purulent sputum. The anteroposterior diameter of the thorax was increased slightly and expansion of the chest was limited. Breath sounds were everywhere diminished and accompanied by showers of fine rales. There was marked accentuation of the second pulmonic sound.

X-ray of the chest (Fig. 7) showed diffuse finely nodular infiltration of both lungs. During nineteen months in the hospital her dyspnea increased and her cough became productive of sputum which was purulent and at times foul. Therapy with oxygen and antibiotics produced no significant change in her condition. She was transferred to another hospital for chronic care. Death from progressive respiratory failure complicated by hemoptysis occurred about seven months after this transfer. Autopsy showed widespread pulmonary fibrosis involving the alveolar-capillary septa. (Fig. 15.) This fibrosis was of non-specific character, but a few tiny islands of granulomatous lesions characteristic of Boeck's sarcoid were found within it. There was widespread bronchiolectasis in both lower lobes. Granulomatous lesions characteristic of Boeck's sarcoid were present in the liver and spleen.

CASE VIII. F. L. was a thirty-nine year old electrician admitted to the hospital on October 30, 1950. In the five years preceding admission he had broken many fluorescent bulbs and was thus exposed to beryllium phosphors. Two years before admission a chest x-ray was said to show a diffuse pulmonary infiltration. Nine months prior to admission he developed an acute respiratory illness and a diagnosis of "virus pneumonia" was made. Following this he had a persistent dry cough and exertional dyspnea. Physical examination showed a healthy looking man who was breathing rapidly. There was cyanosis, rales over the lower half of the chest posteriorly and marked clubbing of fingers.

X-ray of the chest revealed a uniform nodular infiltration involving both lung fields. (Fig. 8.) Treatment with cortisone was started. The details of this therapy will be reported at a later date. During seven weeks of hospitalization there was a steady increase in exertional dyspnea. About ten days before his death he complained of chest pain. An increase in his sputum, more cyanosis, fever to as high as 103°F, an elevated white blood count and an increase in the number of rales were noted. Bronchopneumoina was believed to be present and therapy with antibiotics and oxygen was started. Two days before his death a rapid cardiac rate and a diastolic gallop were present. Electrocardiogram showed evidence of acute cor pulmonale. His condition deteriorated rapidly and he died of cardiorespiratory failure about ten months after his first significant symptom and two months after leaving full-time work.

Autopsy showed diffuse pulmonary fibrosis with a marked increase in the thickness of the alveolar-capillary septa. (Fig. 16.) No granulomatous lesions were found in the lungs or lymph nodes. Beryllium could not be identified spectrographically in the lungs but was identified in the hilar lymph nodes. The lungs showed bronchiolectasis in both lower lobes and there was evidence of terminal bronchopneumonia.

CASE IX. F. S. was a forty-three year old

white man who entered the hospital on September 13, 1948, complaining of cough and shortness of breath. Except for a ten-year history of "sinusitis" he had enjoyed good health. In the three years before admission he had developed an increasing and productive cough as well as progressive dyspnea. He had also lost 25 pounds. He gave no history of exposure to toxic agents. Physical examination showed a tachypneic, chronically ill man. The anteroposterior diameter of the chest was slightly increased and expansion of the thorax was limited. Fine rales were present over both lungs. The second pulmonic sound was accentuated. There was moderate clubbing of the fingers and toes.

X-ray of the chest (Fig. 9) showed extensive diffuse reticular infiltration throughout both lungs, more marked on the right. There was no clinical change during hospitalization of two months and he was discharged to his home.

CASE X. E. M. was a sixty year old colored woman admitted to the hospital on November 13, 1947. She had been well until a year before hospitalization when she developed exertional dyspnea and a non-productive cough. Physical examination showed only persistent rales at both lung bases.

X-ray of the chest (Fig. 10) showed a linear and patchy infiltration throughout both lung fields but greater on the right where there was also evidence of some pleural fibrosis. There was no significant change in her clinical status during hospitalization for three months and she was discharged to her home.

CASE XI. M. H., a sixty-four year old white woman, had had for the twenty years preceding admission a chronic non-productive cough and periodic episodes of acute respiratory illness. Dyspnea on exertion, which increased in its severity progressively, was first noted about seven years before admission. Two months before entering Bellevue Hospital, on March 28, 1950, ankle edema was noted at another hospital. Physiologic studies there revealed pulmonary hypertension, an elevated right ventricular end diastolic pressure, polycythemia and arterial oxygen unsaturation. Digitalization and phlebotomies were followed by loss of edema. Another acute episode led to her entry to Bellevue. On physical examination the positive findings were fever of 101°F., tachypnea, cyanosis, rales over the lower portions of both lungs, an accentuated pulmonic second sound, an enlarged liver and marked clubbing of the fingers. The electrocardiogram showed peaked P waves in lead II and digitalis effect.

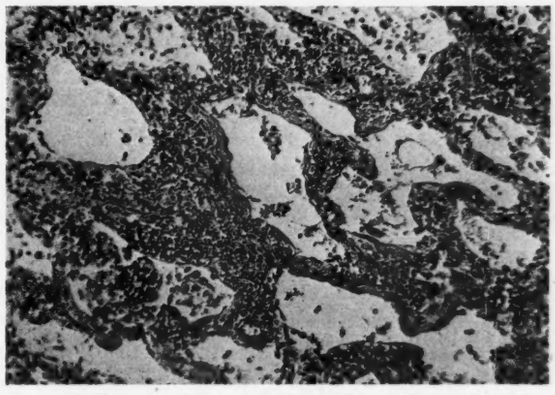

FIG. 17. Case XII. Microscopic section of lung of J. Hi.; pulmonary granulomatosis after exposure to beryllium; hematoxylin and eosin stain; × 200.

X-ray of the chest revealed a widespread nodular infiltration (Fig. 11) throughout both lung fields. On penicillin and aureomycin her temperature returned to normal by the fourth hospital day. Digitalis and mercurial diuretics were also given, with considerable improvement in her dyspnea. She left the hospital after a few weeks and is known to have died at home four months later with symptoms of severe respiratory insufficiency.

CASE XII. J. Hi., a sixty-six year old white male electrician, was admitted to the hospital on June 6, 1949, complaining of shortness of breath, weakness and loss of appetite of six weeks' duration. Twenty years previously he had been shot in the left chest and the bullet remained embedded in the chest wall. For nine years, as a result of breaking fluorescent light bulbs, he had been exposed to beryllium phosphors and for several years he had had cough productive of 1 to 3 ounces of clear mucoid sputum daily. This symptom became somewhat worse before admission and was accompanied by slight dyspnea at rest and marked dyspnea on mild exertion. In addition, the patient lost 30 pounds in the six months before hospitalization. On physical examination the patient showed poor nutrition, tachypnea, slight cyanosis, limited chest expansion with an increased anteroposterior diameter, rales at both bases, an accentuated pulmonic second sound and clubbing of the fingers. The electrocardiogram revealed alternating left and right bundle branch block.

X-ray of the chest showed dense homogeneous infiltrations of a reticular type involving the

lower two-thirds of both lung fields, more marked on the right. (Fig. 12.) Two months after study he developed a right spontaneous pneumothorax. Despite re-expansion of the right lung he grew progressively more dyspneic and dependent upon oxygen therapy. He died of respiratory failure five months after study.

At autopsy the lungs were nodular and lacked normal crepitation. There was evidence of marked interstitial thickening with preservation of the air spaces. In addition the upper lobes showed confluent areas of fibrosis obliterating the normal pulmonary architecture. Sections of the lungs showed two types of pathologic processes. At the apices the parenchyma was replaced by proliferating granulation tissue infiltrated with lymphocytes, plasma cells and mononuclear cells and contained Langhans and foreign body giant cells. The few remaining air spaces were reduced to narrow slits. In sections from the basal portions of the lungs the outlines of pulmonary architecture were preserved but the alveolar walls were thickened markedly by similar granulation tissue with resultant reduction of the alveolar air spaces. (Fig. 17.) An additional finding of interest was the presence in all sections of the lungs of marked encroachment upon the lumen of pulmonary arteries by intimal proliferation.

SUMMARY

1. Twelve additional cases with various diffuse diseases of the lungs characterized physiologically principally by interference with the diffusion of oxygen across the alveolar-capillary septum have been studied.

2. The patients in this group included two with pulmonary granulomatosis following exposure to beryllium; one with pulmonary granulomatosis of the Boeck's sarcoid type; one with pulmonary granulomatosis of undetermined etiology, in which the granulomatous lesion contained unusually large numbers of foreign body-type giant cells and bi-refractile crystals; one patient with scleroderma; three patients with pulmonary fibrosis of unknown etiology (in one case after exposure to beryllium, in two cases associated with granulomas in other organs), and four cases in which a diagnosis could not be made.

3. The pattern of pulmonary dysfunction consisted of (1) reduced lung volumes, (2) maintenance of a large maximum breathing capacity, (3) hyperventilation at rest and during exercise, (4) normal or nearly normal arterial oxygen saturation at rest but a marked reduction of the arterial oxygen saturation after exercise, (5) normal alveolar oxygen tension, (6) a reduced oxygen diffusing capacity and (7) pulmonary artery hypertension.

4. In some severe cases the dead space-like ventilation and the venous admixture-like perfusion was increased. These findings have been interpreted as an indication of the inhomogeneous nature of the pathologic process.

5. The clinical findings have been analyzed in the light of the physiologic data and the evolutionary trends, both clinical and physiologic, have been described.

6. Because the major pathologic changes are localized in the alveolar capillary septa and because the major physiologic defect is a reduction of the permeability of the alveolar capillary membrane for oxygen, the name "alveolar-capillary block" has been tentatively offered to describe this syndrome.

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Primary Pulmonary Hypertension*

I. Clinical and Hemodynamic Study

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PULMONARY hypertension is known to occur in association with left heart failure, chronic pulmonary disease, certain types of congenital heart disease (especially those with increased pulmonary blood flow), diffuse pulmonary embolism, kyphoscoliotic heart disease and specific affections of the pulmonary vascular bed. There is also a primary form of pulmonary hypertension, which is defined as that condition in which an elevated pulmonary artery pressure exists without demonstrable cause. We believe that primary pulmonary hypertension, which has emerged as a distinct entity since the advent of right heart catheterization,[1] is the cause of isolated right ventricular hypertrophy[2–23] whether or not associated with pulmonary vascular sclerosis.

Hypertrophy of the right ventricle in the absence of the previously mentioned disorders was reported by Romberg[24] in 1891. There has been considerable speculation concerning the primary role of pulmonary hypertension[12,16–19] in this condition. Since pulmonary vascular sclerosis was not constantly found, doubt was cast on hypertension in the lesser circulation as the cause of the right ventricular hypertrophy. De Navasquez et al.,[17] for example, preferred to designate their cases as "idiopathic right ventricular hypertrophy" rather than introduce the concept of pulmonary hypertension since no significant changes were found in the pulmonary blood vessels in their cases at necropsy.

Autopsied cases which we consider to fall into the category of primary pulmonary hypertension have been reported under various titles, such as "primary pulmonary vascular sclerosis,"[13,18,21] "right ventricular hypertrophy of unknown origin: so-called pulmonary hypertension,"[17] "isolated hypertrophy of the right ventricle of the heart of unknown cause."[20] These titles stressed different facets of the pathophysiologic features of this disease. All cases showed marked right ventricular hypertrophy, but the nature, distribution and severity of the pulmonary vascular changes proximal to the capillaries showed considerable variation. The predominant changes were atheromatous lesions of the stem and large elastic arteries, alone or in conjunction with fibrous intimal thickening and narrowing of the smaller arteries and arterioles. Medial hypertrophy was occasionally noted. In about half of the reported cases occlusive lesions of the smaller arteries and arterioles were described. Most of these changes have been ascribed to intimal sclerosis and some to thrombi in various stages of organization. A small group remains in which the pathogenesis of the occlusive lesions cannot be definitely established and may conceivably represent organized pulmonary emboli or healed inflammatory lesions. The last group, of course, would not fit into the category of primary pulmonary hypertension. Whether the obliterative sclerosis or thrombosis, when seen, is the cause or the effect of the hypertension has evoked considerable difference of opinion. Arguments against the primary role of the vascular changes are (1) the absence of these findings in some cases of isolated right ventricular hypertrophy,[6,12,14,16,17,20,22] one of which was proven to have pulmonary hypertension by heart catheterization,[22] and (2) the finding of pulmonary arteriosclerosis unassociated with right ventricular hypertrophy.[13]

Ten[22,25–27] catheterized cases of pulmonary hypertension without demonstrable cause have been mentioned in the literature. Although Nellen[28] reported two cases with hemodynamic studies as "idiopathic pulmonary hypertension," they are not included because of extensive thromboses involving the major pulmonary

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arteries. In only three of the ten cases were hemodynamic studies reported. The data were limited to pressure determinations in the pulmonary artery or right ventricle or both.

Prior to the introduction of heart catheterization technics this disease was considered to be rare. In 1931 MacCallum[11] reported one case in 12,000 autopsies at the Johns Hopkins Hospital. In 1939 Killingsworth[15] reported one case in 2,707 necropsies at the Children's Memorial Hospital in Chicago. Since heart catheterization has become an accepted procedure, the diagnosis of primary pulmonary hypertension is being made more frequently than such statistics would imply. Wood,[26] in England, studying a group of 233 unselected cases of suspected congenital heart disease, 152 of whom were catheterized, found six cases which he classified as "idiopathic pulmonary hypertension." Chapman[25] in a similar study so diagnosed two of seventy-two patients in whom right heart catheterization was performed. In our experience four cases were encountered over a two-year period at a 500-bed general hospital. Heart catheterization was performed in three of these four patients and the details of these studies will be presented. The clinical course and pathologic findings of the other patient were characteristic of the disease under discussion.

CLINICAL PICTURE

Primary pulmonary hypertension has been described in a patient as young as twenty months[21] and in one as old as seventy-four years,[11] the majority of the cases falling in the age group between twenty and forty years. Sixty per cent of the cases reviewed, in which the sex was stated, were females.

Brenner[13] in reviewing this subject stated that the disease appeared to run a course of from five months to five years, with an average course of two years. MacCallum[11] reported a patient who died fifteen years after onset of symptoms. The disease usually runs a progressive downhill course characterized by right heart failure, not infrequently terminating in sudden death.[7,13,15,18,19] The heart failure apparently is not favorably influenced by digitalis.

The salient clinical features in a series of thirty-nine reported cases[2–23] were, in order of frequency, exertional dyspnea and weakness, substernal and left chest pain with exertion resembling angina, syncope on exertion, palpitations, orthopnea and hemoptysis. On physical examination these patients were described as showing variable degrees of cyanosis without clubbing of the fingers. Orthopnea was rarely noted. The lungs were generally described as clear, except terminally when basal rales have been reported. Percussion of the heart revealed increased substernal dullness and widening of the conus area. The rhythm was regular in all but one case[16] in which transient auricular fibrillation was noted terminally. Systolic murmurs have usually been noted at the apex or pulmonic area. Diastolic murmurs at the pulmonic area have also been mentioned. The second pulmonic sound was greatly accentuated in all cases. Protracted neck-vein distention, elevated venous pressure and hepatomegaly were frequently observed, unassociated with peripheral edema which was usually a late finding.

Except for cyanosis, orthopnea and hemoptysis, the findings in our cases conform to those described in the literature. An impressive feature in two of our cases was the contrast between the appearance of good health when at rest and the striking discomfort evoked by even mild exertion.

Roentgenograms in our patients and in those reviewed show certain characteristic features which, although not specific, were highly suggestive of this disease. There was evidence of right ventricular enlargement. The conus and the pulmonary arterial trunk including its major branches were prominent, whereas the intrapulmonary vascular markings were normal or decreased. There was no evidence of left atrial enlargement. Electrocardiograms were consistent with right ventricular hypertrophy.

Routine examinations of the blood and urine were generally helpful only in that they were within normal limits. Although a slight degree of polycythemia[9,16] has been noted, it was not present in our cases.

CASE REPORTS

CASE I. G. N., a twenty-five year old married Czechoslovakian female, was admitted to the Maimonides Hospital on January 10, 1950, because of exertional weakness, dyspnea and effort syncope of six years' duration. Substernal and epigastric pain was provoked by mild exertion which, if continued, would result in syncope lasting two to five minutes. There was no associated incontinence or tongue biting. There was no history of dependent edema, orthopnea, cyanosis, pulmonary disease, systemic hyper-

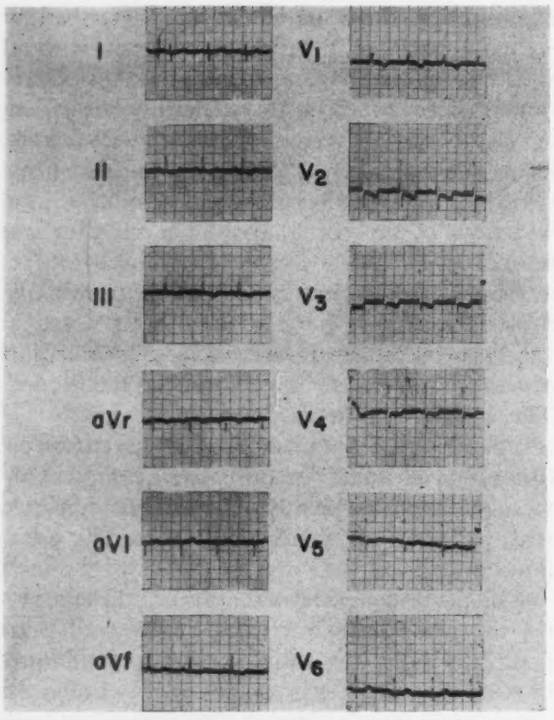
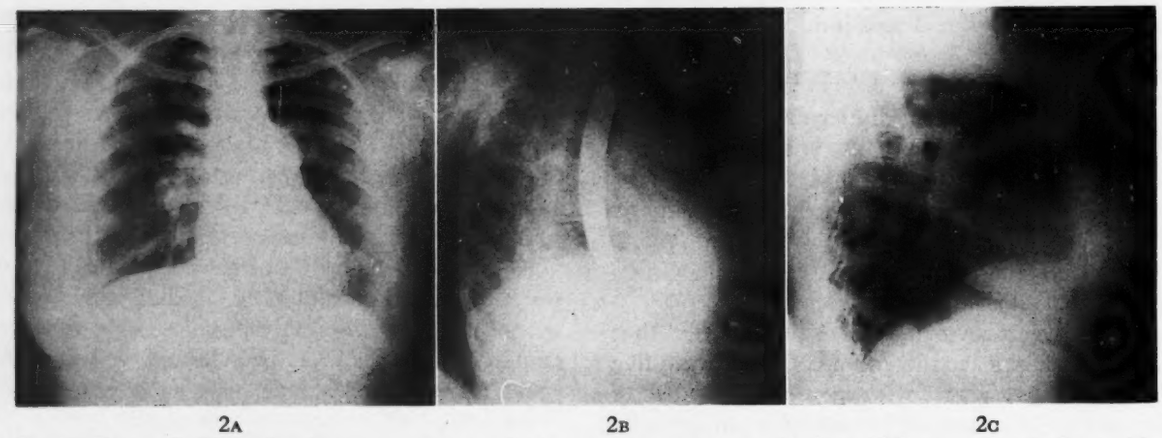


FIG. 1. Case 1, G. N. (February 16, 1950.) The pattern of right ventricular hypertrophy is shown by the delayed intrinsicoid deflection in V_1 and the tall R waves, depressed S-T segments and inverted T waves in V_{1-4}.

obese, robust young female who appeared somewhat younger than her stated age. The systemic blood pressure was 120/70, pulse 99, temperature 99°F. She seemed comfortable at rest and there was no cyanosis, clubbing or dependent edema. Funduscopic examination was normal. The neck veins were not distended and the thyroid was not enlarged. The lungs were clear to percussion and auscultation. The heart was not enlarged to percussion and the heart action was regular. A diastolic shock could be felt over the pulmonic area. The second pulmonic sound was split and greatly accentuated. No murmurs were heard. The liver and spleen were not palpably enlarged. There were good arterial pulsations in the lower extremities.

Laboratory studies: urinalysis, negative; hemoglobin, 13 gm. per cent; red blood cell count, 4.55 million; white blood cell count, 8,000 with a normal differential. Erythrocyte sedimentation rate (Wintrobe) was 14 mm. in one hour. The Mazzini test was negative. Fasting blood sugar was 60 mg. per cent; blood urea nitrogen, 20 mg. per cent. Total proteins were 8.2 gm. per cent, albumin, 4.7 gm. per cent and globulin, 3.5 gm. per cent. The blood cholesterol was 212 mg. per cent with 24 per cent free; blood



2A 2B 2C

FIG. 2. Case 1, G. N. A, showing a prominent pulmonary artery segment and enlarged hilar vascular shadows with clear lung fields; B, the barium-filled esophagus in the right anterior oblique view shows no posterior displacement; C, diffuse dilatation of the pulmonary artery is noted in the lateral view.

tension or thromboembolic phenomena. She had been treated at various clinics, European and American, for these complaints without improvement. There was no past history of rheumatic fever, chorea, scarlet fever or nephritis. The family history was non-contributory, except for a twin sister who died in infancy of a "cold."

Physical examination revealed a short, slightly

calcium, 7.0 mg. per cent; phosphorus, 3.6 mg. per cent. The cephalin flocculation test was negative. Venous pressure on two separate occasions was 100 and 110 mm. of saline and the decholin circulation time was nineteen seconds. The electrocardiogram (Fig. 1) was consistent with right ventricular and right atrial hypertrophy. Chest x-rays are shown in Figure 2A to 2C.

The patient's course in the hospital was uneventful. Exercise tolerance was self-limited to three to four successive stair steps. The diagnosis of primary pulmonary hypertension was suggested. Because of the x-ray findings and limited exercise tolerance, heart catheterization was performed.

CASE II. M. R., a 35 year old Puerto Rican housewife, was admitted for the first time to the Maimonides Hospital on April 17, 1950, because of pharyngitis. She was apparently well until the delivery of her fifth child four years prior to this admission. As far as could be determined the first record of her ante-partum status was made during the seventh month of this pregnancy. Blood pressure was 120/88 and no heart murmurs were described. Urinalysis was negative. The patient complained of some exertional dyspnea at this time. Two months later prior to the onset of labor blood pressure was 138/98 and a "to and fro" murmur was heard at the apex. Following the spontaneous delivery of a normal male infant and before the expulsion of the placenta she had a generalized convulsive seizure which lasted one and one-half minutes. The sensorium was clouded for the ensuing fifteen minutes. Blood pressure immediately following the convulsion was 90/70 and the pulse was 160 beats per minute. There was no chest pain or hemoptysis. Recovery was rapid and uneventful. About two weeks after delivery the patient noted swelling of the face, abdomen and legs without respiratory difficulties. She was admitted to another hospital five months later for these complaints. She was digitalized and given weekly mercurial diuretics. Two and one-half years later progressive exertional dyspnea and orthopnea appeared. Fleeting chest pain on exertion was noted. She had no syncope, chronic cough, hemoptysis or thromboembolic phenomena. There was no past history of rheumatic fever, chorea, scarlet fever, nephritis or toxemia of pregnancy.

Physical examination disclosed a well developed and well nourished female in no distress. The systemic blood pressure was 165/85, pulse 80, temperature 99°F. There was evidence of mild pharyngitis. The retinal vessels showed minimal sclerotic changes. The neck veins were distended and pulsating. The lungs were clear to percussion and auscultation. The point of maximal impact of the heart was in the sixth intercostal space, 2 cm. outside the mid-clavicular line. There was a pre-systolic apical thrill and a grade III, harsh, apical diastolic blow which was widely transmitted and well heard at the lower sternum. A grade III, apical systolic murmur was widely transmitted and heard equally well over the lower sternum. The pulmonic second sound was accentuated and was louder than the aortic second sound. A slightly tender liver edge was felt 6 cm. below the costal margin. There was no cyanosis, clubbing or edema. The heart action was regular.

Laboratory studies revealed: urinalysis, negative except for an occasional trace of albumin; hemoglobin, 14.5 gm. per cent; red blood cell count, 4.69 million; white blood cell count, 16,000 with a shift to the left initially, returning to normal. The erythrocyte sedimentation rate (Wintrobe) was 4 mm. per hour. Blood chemistries showed: fasting blood sugar, 65 mg. per cent; blood urea nitrogen, 13 mg. per cent; total proteins, 6.9 gm. per cent, albumin, 3.6 gm. per cent, globulin, 3.3 gm. per cent; total cholesterol, 161 mg. per cent with 25 per cent free; blood calcium, 9.8 mg. per cent; cephalin flocculation test, negative; thymol turbidity, 2.8 units; blood sodium, 142.8 mEq./L.; chlorides, 105.5 mEq./L. and potassium, 5.1 mEq./L. The blood Mazzini test was negative. The venous pressure was 145 mm. of saline with a positive hepatojugular reflux. The decholin circulation time was thirty-one seconds and the ether circulation time was eleven seconds. The electrocardiogram (Fig. 3) was consistent with right ventricular hypertrophy. Chest x-rays are shown in Figures 4A to 4C.

The pharyngitis responded promptly to penicillin. The patient improved on bed rest, salt poor diet, digitoxin and mercurial diuretics. Nine days after admission the venous pressure was 110 mm. of saline. The diastolic murmur heard initially became inaudible during the third week of hospitalization. Because of the unusual x-ray findings, changing murmurs and lack of left atrial enlargement she was referred to the cardiopulmonary laboratory for heart catheterization. As a result of these studies and the clinical findings this patient was thought to have rheumatic heart disease with mitral stenosis and insufficiency and a pulmonary endarteritis. She was then discharged on a cardiac regimen.

The patient was readmitted to the Maimonides Hospital three months later because of increasing heart failure responding poorly to digitoxin and mercurial diuretics. Dyspnea became more marked during the two days prior to admission.

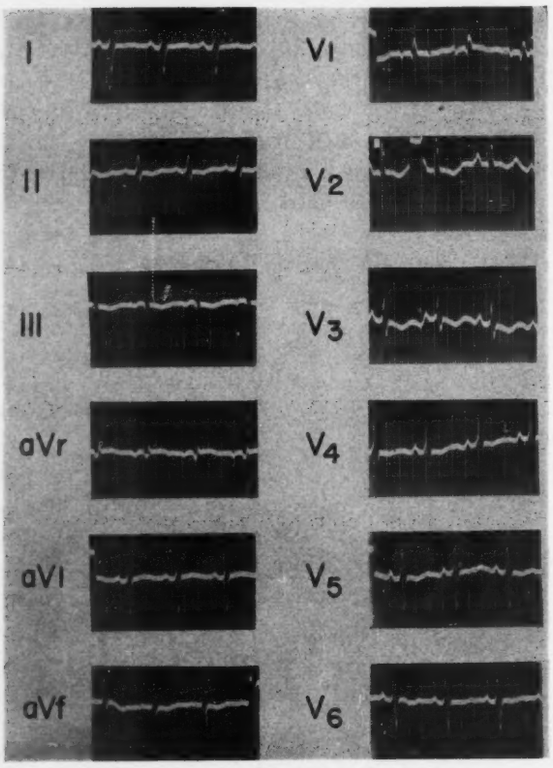
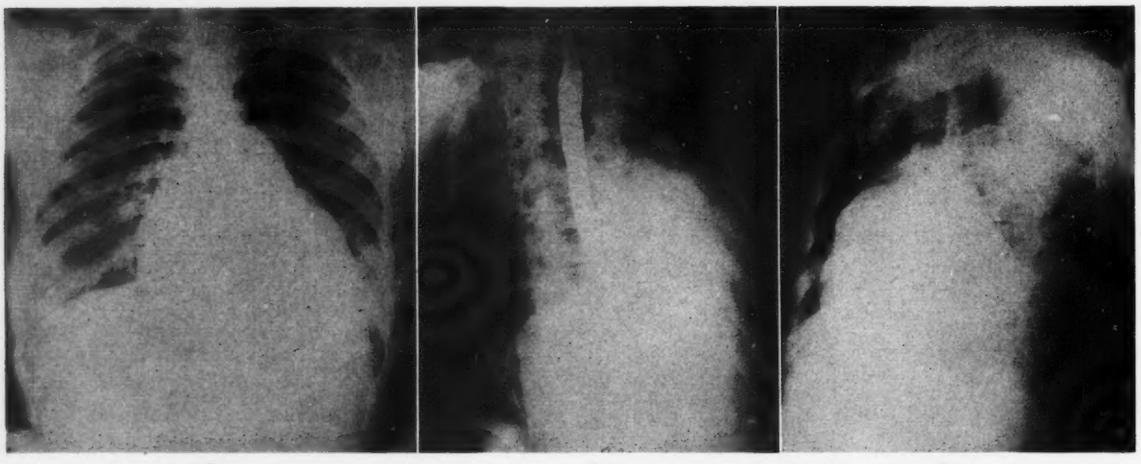


FIG. 3. Case II, M. R. (May 12, 1950.) There is a Q wave and delay of the intrinsicoid deflection in V_1 and an R wave in aVr.

hepatojugular reflux. The lungs were clear to percussion and auscultation. The heart action was irregular with a pulse deficit, the radial rate being 56 beats per minute. No diastolic murmurs were heard. The liver edge was felt four finger breadths below the costal margin. There was three plus ankle edema extending to the mid-calf. The nail beds were dusky.

Laboratory studies were essentially unchanged. The white blood cell count was 12,200. The electrocardiogram showed ventricular premature contractions in addition to the signs of right ventricular hypertrophy.

The patient was placed on bed rest, a salt-free diet, mercurial diuretics and digitoxin. Digitoxin was discontinued after the second dose because of the onset of bigeminal rhythm and vomiting. The venous pressure was 242 mm. of saline with a positive hepatojugular reflux. The decholin circulation time was thirty-seven seconds. Following estimation of the ether circulation time the patient developed nausea. The following day the patient's condition deteriorated with the onset of retching, feeble pulse and a sinus tachycardia of 120 beats per minute. There was no dyspnea or orthopnea. Five hours later she was pulseless, cool, cyanotic and the blood pressure

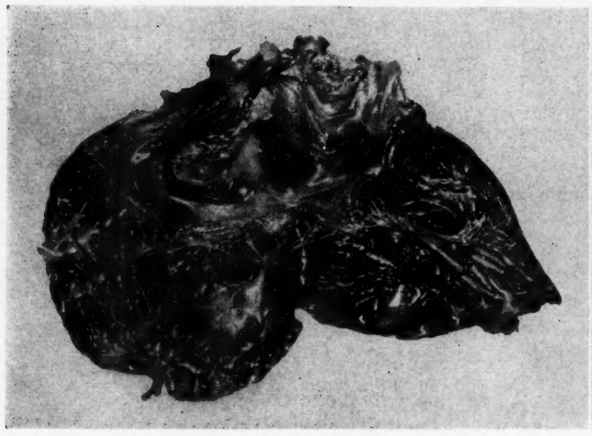


4A 4B 4C

FIG. 4. Case II, M. R. A, showing enlargement of the heart to the left and inferiorly with rounding of the cardiac apex above the diaphragm and increased convexity of the pulmonary artery segment. The hilar vessels are enlarged whereas the intrapulmonary vascular markings are diminished; B, enlargement of the right ventricle but there is no displacement of the barium-filled esophagus in the right anterior oblique view; C, the left ventricle overlaps the spine in the left anterior oblique view. The left ventricle was normal at necropsy.

There was no cough, chest pain or hemoptysis. On physical examination the patient appeared in no acute distress. Blood pressure was 130/95 and the temperature 99.2°F. The neck veins were distended and pulsating with a positive

was unobtainable. A portable chest film showed the lung fields to be clear. She was placed in an oxygen tent and given an infusion containing neosynephrine without demonstrable effect. The cyanosis was relieved by oxygen adminis-



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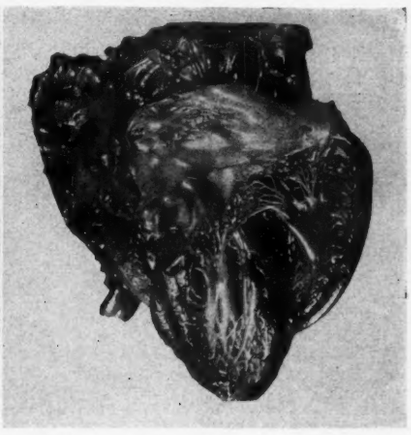

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FIG. 5. Case II, M. R. The right atrium is dilated. Marked dilatation and hypertrophy of the right ventricle with scattered patches of endocardial thickening is seen.
FIG. 6. Case II, M. R. The left atrium, left ventricle and mitral valve are normal.

tered either by tent or mask. She failed to respond to therapy and died sixteen hours after the onset of cardiovascular collapse.

Autopsy* was performed sixteen hours after death through a limited abdominal incision. The pericardial cavity and its lining were normal. The heart weighed 330 gm. The right atrium and ventricle were dilated. The right atrium was thin whereas the right ventricle was markedly hypertrophied (Fig. 5) and measured 0.9 cm. in thickness. The left atrium and ventricle (Fig. 6) were normal. The left ventricle measured 1.4 cm. in thickness. The interventricular septum was hypertrophied and bulged somewhat into the left ventricle. The valvular circumferences were as follows: tricuspid, 11.5 cm.; pulmonic, 7.0 cm.; mitral, 8.0 cm. and aortic, 6.0 cm. There were no abnormalities of the valve leaflets or cusps. The coronary arteries including their ostia were normal. The pulmonary artery and its major branches were dilated and showed widespread atheromatous plaque formation. The aorta was normal. No congenital malformations were found.

A small amount of fluid was present in each pleural space. The pleural surfaces were smooth and glistening. The lungs appeared normal except for some atelectasis of the left lower lobe. The right lung weighed 310 gm. and the left lung weighed 335 gm. No thrombi or emboli were noted in the pulmonary vessels.

The liver weighed 1,240 gm. and aside from a characteristic "nutmeg" appearance presented no other abnormalities. No other essential organ changes were noted.

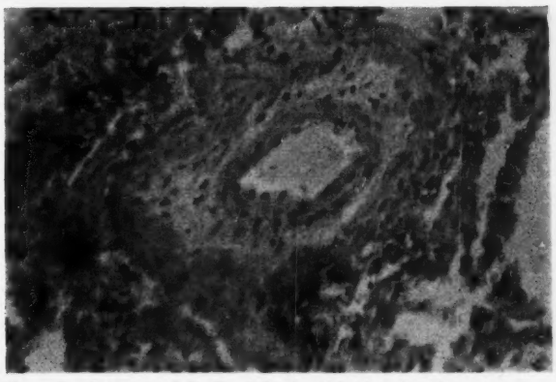
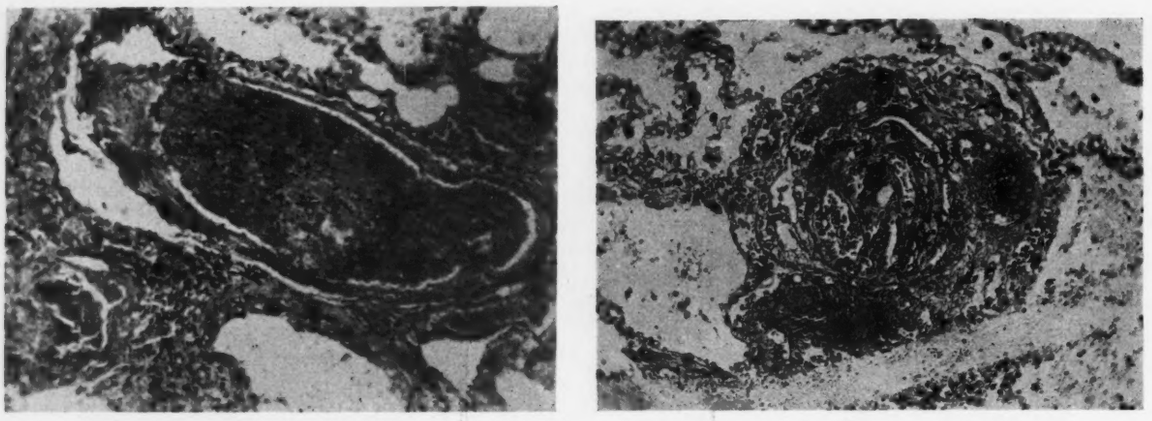


FIG. 7. Case II, M. R. Marked intimal sclerosis of a small intrapulmonary artery is noted; × 300.

Histologically, sections of the heart showed hypertrophy of the muscle fibers of the right ventricle. There was no evidence of myocardial fibrosis or valvular disease.

Multiple sections from various portions of the lungs were examined. Widespread sclerotic changes were noted in the pulmonary arterial tree, varying in degree even in vessels of similar caliber. Plaque formation with intimal thickening as well as increase in the width of the media were noted in the largest vessels. Subintimal thickening and proliferation were the prominent changes in the vessels of microscopic size. (Fig. 7.) In many such vessels the lumen was extremely narrow, at times slit-like. In addition to the above changes there were thrombotic lesions in various stages of organization. They ranged from recent thrombi (Fig. 8A) to re-

* We are indebted to Dr. A. Kantrowitz, Director of the Pathological Laboratories, Maimonides Hospital of Brooklyn, for his kind assistance in the preparation of the autopsy report.



8A 8B

FIG. 8. Case II, M. R. A, a thrombus of recent origin in a pulmonary vessel of microscopic size is seen; × 150. B, a recanalized thrombus in a pulmonary vessel of microscopic size is seen; × 250.

canalized thrombi (Fig. 8B) in the precapillary and post-capillary vessels of microscopic size. These latter changes were much less numerous than the sclerotic changes previously described. All sections revealed normal vessels although those affected seemed to be present in preponderant number.

The bronchi and peribronchial tissues showed no evidence of chronic inflammatory changes. The alveoli revealed no morphologic changes and no "heart failure" cells were seen. The alveolar septal interstitial tissue was not thickened. Sections from the basilar portion of the right lower lobe revealed a slight amount of intra-alveolar edema fluid. Slight atelectasis was noted in sections from the left lower lobe.

Sections of the liver and spleen revealed only marked chronic congestive changes. The remainder of the microscopic examination was normal.

The anatomic diagnoses were: (1) Severe pulmonary arteriosclerosis and arteriolarsclerosis; (2) hypertrophy and dilatation of the right ventricle; (3) old and recent thromboses of the pulmonary arterioles and venules; (4) chronic passive congestion of the liver and spleen; (5) moderate edema of lower lobe of right lung and (6), atelectasis of lower lobe of left lung.

In summary, the autopsy revealed right ventricular hypertrophy and widespread pulmonary vascular sclerosis unassociated with intrinsic lung disease. A preponderance of sclerotic changes over thrombotic lesions in the small pulmonary vessels was evident.

CASE III. M. K., a thirty-four year old white housewife, was admitted to the Maimonides Hospital on July 17, 1950, because of weakness, exertional dyspnea and numerous syncopal episodes of two years' duration. Syncope occurred only during exertion and was frequently preceded by great weakness. It was never accompanied by convulsions or tongue biting. Hyperventilation was denied. There was no history of orthopnea or cyanosis. A complete medical study including chest x-ray, electrocardiogram, electroencephalogram and blood studies at another institution was reported as normal. The patient was then advised to seek psychiatric aid. Intermittent ankle edema, epigastric pressure on exertion, transient nausea, vomiting and diarrhea appeared two months before admission. One day prior to admission she lost consciousness and incurred a contusion of the right eye. Her past history was non-contributory. The patient has two normal children, ages three and eight years, respectively. Pregnancies were uneventful.

Physical examination disclosed a well developed young woman in no distress. The systemic blood pressure was 120/95, pulse 80, temperature 98°F. There was an ecchymosis over the right eye. Dyspnea, orthopnea, cyanosis, clubbing and edema were absent. The neck veins were moderately distended. The lungs were clear to percussion and auscultation. The point of maximal impact of the heart was in the fifth intercostal space at the mid-clavicular line and a pulsatory, heaving impulse was noted in the third intercostal space at the left of the sternum. Retrocardiac dullness was increased. The heart action was regular and the heart sounds were of good quality. The pulmonic second sound was greatly accentuated and was

louder than the aortic second sound. No murmurs were heard. A firm, non-tender liver edge was palpable at the level of the umbilicus.

Laboratory studies showed: urinalysis, negative; hemoglobin, 14.5 gm. per cent; red cell count, 5.1 million; white cell count, 10,100 with a normal differential. Blood chemistries revealed: fasting blood sugar, 75 mg. per cent; blood urea nitrogen, 13 mg. per cent; serum albumin, 4.0 gm. per cent; serum globulin, 2.3 gm.per cent; alkaline phosphatase, 5.8 King-Armstrong units; thymol turbidity, 0.2 units; icteric index, 7.9. The blood Mazzini test was negative. The venous pressure was 200 mm. of saline with a positive hepatojugular reflux. The ether circulation time was four seconds and the decholin circulation time was twenty-five seconds. The electrocardiogram (Fig. 9) revealed a pattern consistent with right atrial and right ventricular hypertrophy. Chest x-rays are shown in Figures 10A to 10C.

In view of the presenting symptoms and physical findings the diagnosis of primary pulmonary hypertension was made. The patient was then referred to the cardiopulmonary laboratory for confirmation of this diagnosis and for hemodynamic studies. During cardiac catheterization the patient was digitalized with lanatoside C. Subsequently she was placed on a maintenance dose of digitoxin and discharged on August 1, 1950. Despite a strict cardiac regimen there was no obvious improvement in her clinical status. She was readmitted two months later for re-evaluation and pharmacodynamic studies. Physical examination was essentially as on the previous admission.

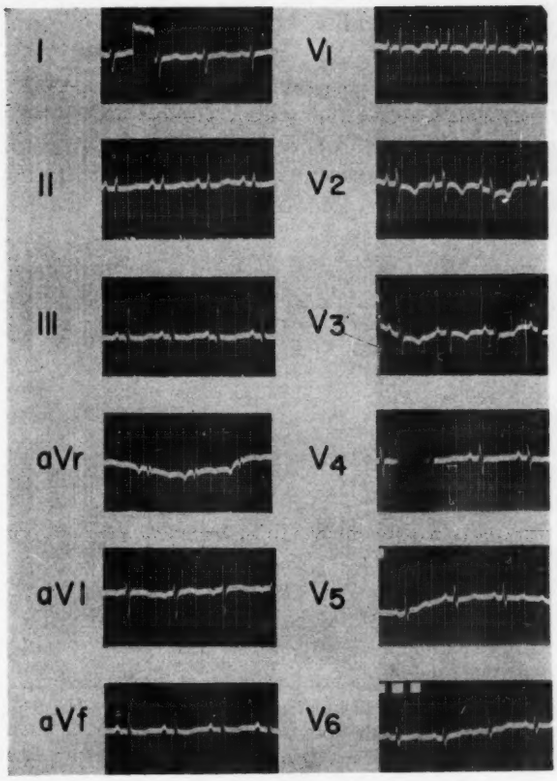
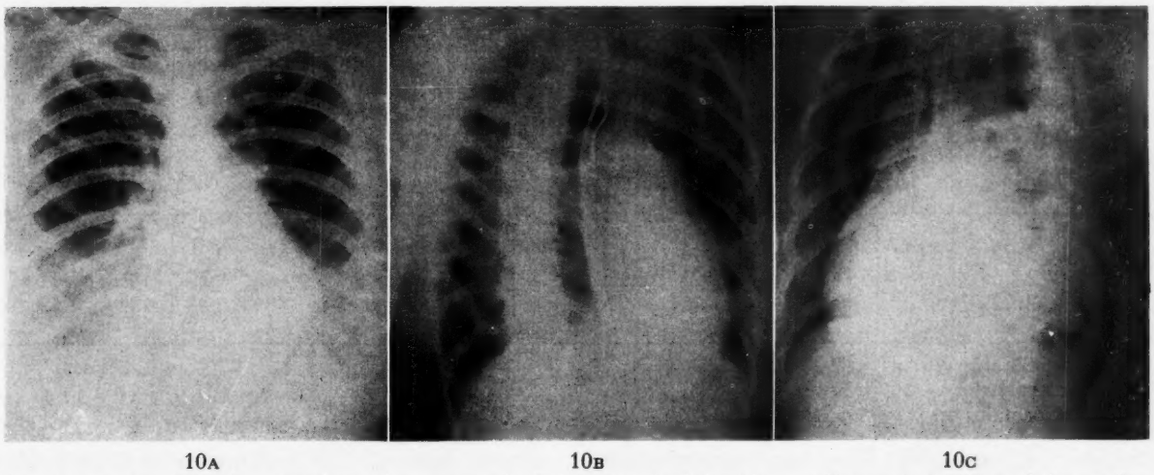


FIG. 9. Case III, M. K. (July 25, 1950.) There are peaked P waves in leads II and III. The R wave in aVr is broad and the R wave in V_1 is high. The T waves are inverted in V_{1-3}. This pattern is consistent with right atrial and right ventricular hypertrophy.



10A 10B 10C

FIG. 10. Case III, M. K. A, showing enlargement of the heart to the left with rounding and elevation of the cardiac apex above the diaphragm. The pulmonary artery segment and hilar shadows are prominent whereas the intrapulmonary vascular markings are normal; B, there is no displacement of the barium-filled esophagus in the right anterior oblique view. The outflow tract of the right ventricle is prominent; C, the left ventricle overlaps the spine in the left anterior oblique view.

Laboratory studies showed: albumin, 4.7 gm. per cent; globulin, 3.9 gm. per cent; total cholesterol, 195 mg. per cent with 20 per cent free; serum calcium, 9.8 mg. per cent; serum phosphorus, 4.3 mg. per cent; serum potassium, 5.8 mEq./L.; serum chlorides, 101 mEq./L.; serum sodium, 145.3 mEq./L.; serum carbon dioxide, 31.5 mEq./L. The bromsulfalein test revealed 15 per cent retention after forty-five minutes. The congo red test was negative.

Following heart catheterization the patient was discharged on October 23, 1950, on a maintenance dose of digitoxin and oral priscoline. She is being followed at the cardiopulmonary laboratory.

HEMODYNAMIC STUDIES

The physiologic data presented in Tables I and II were obtained at the time of right heart catheterization. The patients were studied in a resting state after fasting for at least twelve hours. They received oral phenobarbital 0.06 gm. and nembutal 0.1 gm. the evening before the procedure and phenobarbital 0.06 gm. two

TABLE I

DATA OBTAINED DURING RIGHT HEART CATHETERIZATION

Case No.	Name	Sex	Age	Date	Surface Area (M^2)	Arterial Blood			O_2 Consumption (cc./min.)	BMR (%)	Heart Rate (beat/min.)	Arteriovenous O_2 Difference (vol. %)	Cardiac Output (L./min.)	Cardiac Index (L./min./M^2)	Stroke Volume (cc.)	Blood Volume		
						O_2 Content (vol. %)	O_2 Capacity (vol. %)	Saturation (%)								TBV* (cc./M^2 BSA)	PV† (cc./M^2 BSA)	Hematocrit (%)
I	G. N.	F	25	1-20-50	1.52	18.0	18.4	97.8	217	+12	78	5.9	3.72	2.44	48	2,710	1,615	40
II	M. R.	F	35	5-12-50	1.41	17.7	18.0	98.4	179	+3	94	8.3	2.16	1.53	23	3,550	1,882	47
III	M. K.	F	34	10-10-50	1.71	18.9	19.6	96.4	189	−14	93	6.9	2.72	1.59	29	2,615	1,555	40.5

* TBV = Total blood volume
† PV = Plasma volume

Predicted values (female):

Total blood volume	Plasma volume	Hematocrit
2,670	1,600	40

TABLE II

INTRACARDIAC AND PERIPHERAL BLOOD PRESSURES. RESISTANCES IN PULMONARY AND PERIPHERAL CIRCULATION

Case	Cardiac Output (L./min.)	Peripheral Artery			Systemic Resistance (dynes/cm.^{5}/sec.)		Pulmonary Artery			Pulmonary Resistance (dynes/cm.^{5}/sec.)		Right Ventricle		Right Atrium
		Systolic	Diastolic	Mean	Predicted‡	Observed	Systolic	Diastolic	Mean	Predicted‡	Observed	Systolic	Diastolic	Mean
		(mm. Hg)					(mm. Hg)					(mm. Hg)		(mm. Hg)
G. N.	3.72	117*	79	98	1,440	2,100	121	47	72	221	1,550	121	8	7
M. R.	2.16	135†	91	106	1,560	3,930	73	41	53	239	1,965	75	18	12
M. K.	2.72	113*	80	92	1,280	2,710	90	46	62	197	1,825	84	14	13

* Brachial artery.
† Femoral artery.
‡ See formulas on page 695.

to three hours before any observations were made. Two of the patients, M. K. and M. R., were fully digitalized at the time of the reported studies. M. K. had been digitalized for three months and M. R. for over three years because of earlier clinical findings consistent with congestive heart failure.

The blood oxygen content and capacity were determined by the method of Van Slyke and Neill.[29] The blood volumes were determined by the direct T-1824 (Evans blue) dye method, as modified by Noble and Gregersen.[30] The cardiac outputs and the cardiac indices were determined by the direct Fick principle.[31] Peripheral and intracardiac pressures were recorded using Sanborn electromanometers and a direct writing Sanborn Poly-Viso recorder. The pressures in the pulmonary artery and right ventricle were not recorded simultaneously. Vascular resistances in the pulmonary and systemic circuits were calculated according to the formulas:

$$\text{R. (pulmonary)} = \frac{\text{P.A.m} \times 1.332 \times 60}{\text{C.O.}}$$

$$\text{R. (peripheral)} = \frac{\text{B.A.m} \times 1.332 \times 60}{\text{C.O.}}$$

where R. = vascular resistance in dynes/cm.^{5}/sec.
P.A.m = mean pressure in the pulmonary artery in mm. Hg
B.A.m = mean pressure in the brachial artery in mm. Hg
C.O. = cardiac output in L. per minute

The predicted resistances were obtained using normal mean pressures and blood flows, as reported by Cournand,[32] and corrected for body surface area. The mean pressures were determined by planimetry of the recorded tracings using one or more complete respiratory cycles. The point of zero reference for measurement of intracardiac pressures was 5 cm. below the angle of Louis. The expired air was collected in a Tissot spirometer and was analyzed in the Scholander[33] gas analyzer. The basal metabolic rates were calculated from the observed gas exchange at the time of cardiac output determinations. Pulmonary function studies were performed at a time separate from cardiac catheterization using the technics described by Baldwin et al.[34]

Arterial Blood Oxygen Saturation. The resting arterial blood oxygen saturation was normal in all of the patients. Immediately after maximal exercise there was no change in G. N. and a very slight decrease in M. K. An exercise sample was not obtained in the third patient.

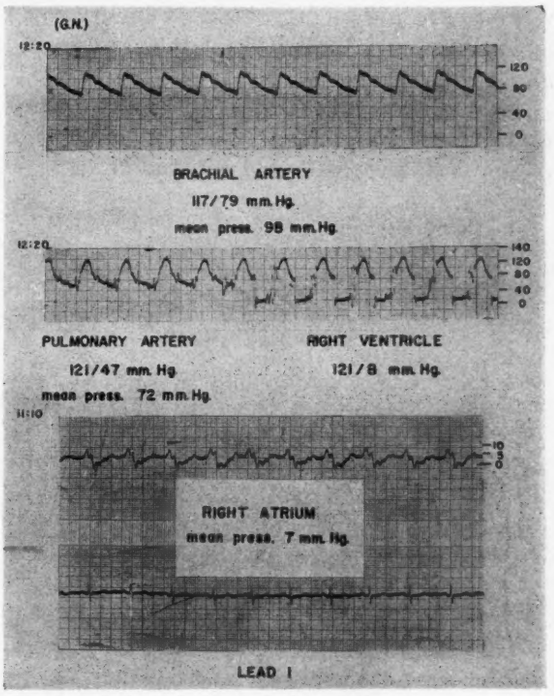


FIG. 11. Case 1, G. N., primary pulmonary hypertension. The brachial and pulmonary artery pressures were taken simultaneously. Continuous tracings during withdrawal of the catheter from the pulmonary artery to the right ventricle showed no change in systolic pressure.

Blood Volume. The total blood volume and hematocrits were normal in G. N. and M. K. and increased in M. R. The total blood volume in M. R. was increased 33 per cent and the hematocrit was 47.

Blood Flow. The cardiac index was low in all of the patients. It was highest but still below the average normal in G. N. The arteriovenous oxygen difference was increased and the stroke volume was decreased in all of the patients.

Arterial and Right Heart Pressures. The peripheral arterial pressures were normal at the time of cardiac catheterization. The pulmonary arterial pressures were markedly elevated. In G. N. the pulmonary systolic pressure was slightly higher than the brachial artery systolic pressure during a simultaneous recording. (Fig. 11.) The right ventricular end diastolic pressures and right atrial pressures were elevated above the accepted normal[35] in all of the patients.

Systemic and Pulmonary Resistances. Pulmonary resistances, calculated from the observed values, averaged eight times the predicted values

whereas the systemic resistances similarly calculated were only twice those predicted. (Table II and Fig. 12.)

Pulmonary Function Studies. Pulmonary function studies were carried out on two of the three patients. (Table III.) The ventilatory capacity was normal in M. K. and reduced in G. N. Oxygen consumption was reduced at rest in M. K. and the rise during exercise was less than expected in both. There was no rise in the oxygen consumption per liter of ventilation during exercise.

TABLE III

PULMONARY FUNCTION AND ARTERIAL OXYGEN SATURATION STUDIES IN TWO PATIENTS WITH PRIMARY PULMONARY HYPERTENSION

Case	Vital Capacity (% of predicted)	Maximal Breathing Capacity (% of predicted)	Ventilation (L./min./M² BSA)		Breathing Reserve (%)			Oxygen Consumption (cc./min./M² BSA)		Respiratory Quotient		Oxygen Intake (cc./L. vent.)		Arterial Oxygen Saturation (%)	
			Rest	Exercise†	Rest	Exercise	1st Min. Recovery	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
G. N.	62	72	4.0	9.2	91	77	74	136	352	.704	.774	34	34	96.8	97.5
M. K.	102	101	2.8	22.1	95	61	78	97	399	.765	.941	35	18	96.2	93.2‡
Predicted*	100	100	3.2	9.0	93	..	79	126	463	.776	.678	45	60	96.2	95.8

* Baldwin et al.[34]

† Exercise—G. N., 23 steps in 1.5 min.
M. K., 24 steps in 1.1 min.

‡ Maximal exercise, supine, during cardiac catheterization.

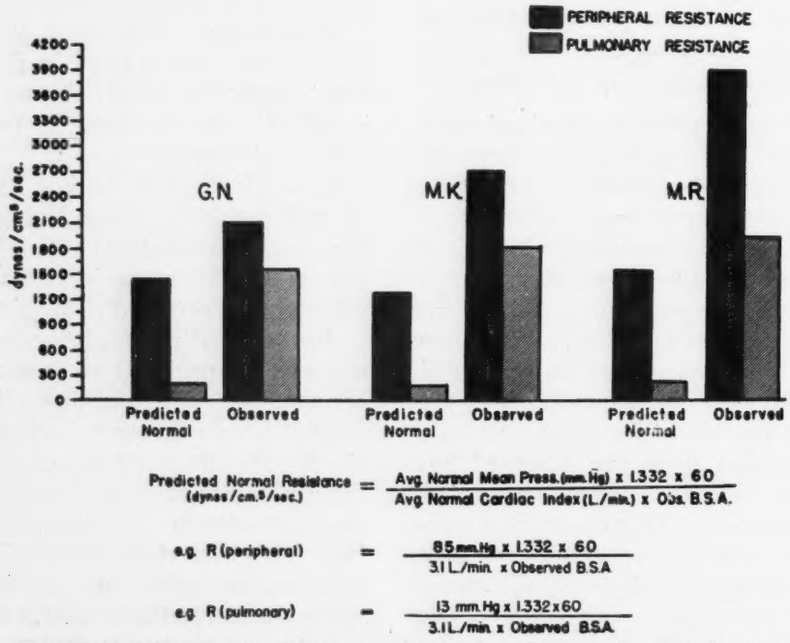


FIG. 12. Peripheral and pulmonary resistance in primary pulmonary hypertension. Calculated pulmonary resistances are seven to nine times those predicted (see procedure).

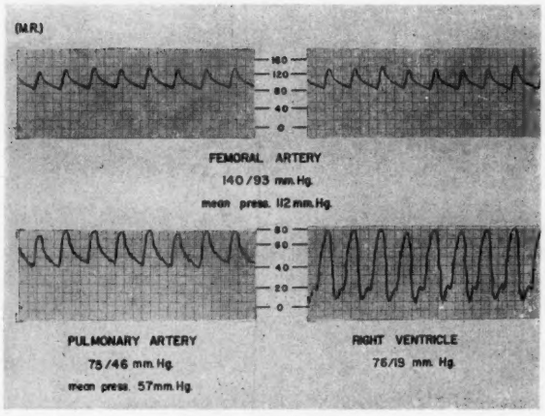


FIG. 13. Case II, M. R. Note the pulmonary hypertension and the elevated right ventricular end diastolic pressure. (The tracings were inked over for photographic purposes.)

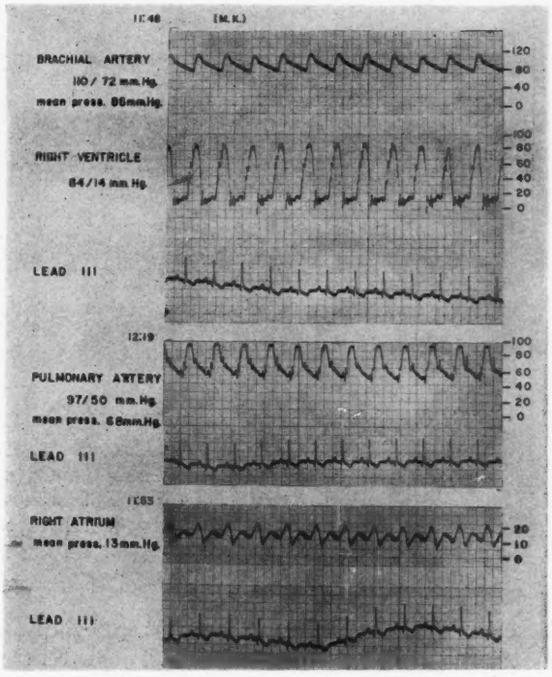


FIG. 14. Case III, M. K. Pulmonary hypertension and elevated right ventricular end diastolic and mean right atrial pressures are observed.

COMMENTS

Pulmonary hypertension of considerable magnitude was observed in our three patients. (Table II, Figs. 11, 13 and 14.) Secondary pulmonary hypertension as defined in the introduction was ruled out by clinical and laboratory studies in G. N. and M. K. and by postmortem examination in M. R.

Although the clinical picture is fairly characteristic in patients with primary pulmonary hypertension, the diagnosis has rarely been made during life. Brill and Krygier[18] in their review of the cases up to 1941 noted that the ante-mortem diagnosis was made in only two of twenty cases. Mention has been made of the current increasing frequency of diagnosis. However, in those patients who do not present exertional syncope, as emphasized by Dressler,[40] or angina, or both, the diagnosis may be obscure. It becomes even more difficult in this group when murmurs are heard ordinarily associated with mitral stenosis. Such was the case in M. R. in whom the diagnosis was not made until necropsy despite cardiac catheterization.

Primary pulmonary hypertension should not be confused with so-called Ayerza's disease, which has never been clearly defined but which is often thought of in connection with pulmonary vascular sclerosis. The patients frequently put into Ayerza's group[36–38] are deeply cyanotic because of the underlying lung disturbance. Although many of the cases falling into the category of primary pulmonary hypertension or primary pulmonary vascular sclerosis have been described as cyanotic[13,16–18] no arterial blood oxygen studies were mentioned. Brill and Krygier[18] went so far as to state that the disproportion of cyanosis to dyspnea differentiated this syndrome from cor pulmonale secondary to lung disease. Our patients were not clinically cyanotic and arterial blood oxygen studies showed normal saturations. Stagnant anoxia due to decreased blood flow could explain the cyanosis so frequently described, especially during the terminal phase of this disease. Another possible cause for cyanosis when seen in primary pulmonary hypertension could be a complicating patent foramen ovale. This could have contributed to the cyanosis in the patient reported by Brill and Krygier. The mechanism of cyanosis in primary pulmonary hypertension with patent foramen ovale would be similar to that described by Engle and Taussig[39] in pulmonic stenosis with patent foramen ovale.

Unexplained dyspnea and weakness, especially if associated with exertional syncope[40] or angina in an otherwise healthy-looking individual with an accentuated pulmonic second sound, should suggest primary pulmonary hypertension. Syncopal attacks, described in 20 per cent[11,13,15,17,18,22,26] of the thirty-nine cases reviewed,[2–23] was an early and presenting complaint in two of our patients. It is interesting to note that the syncopal attacks were precipitated

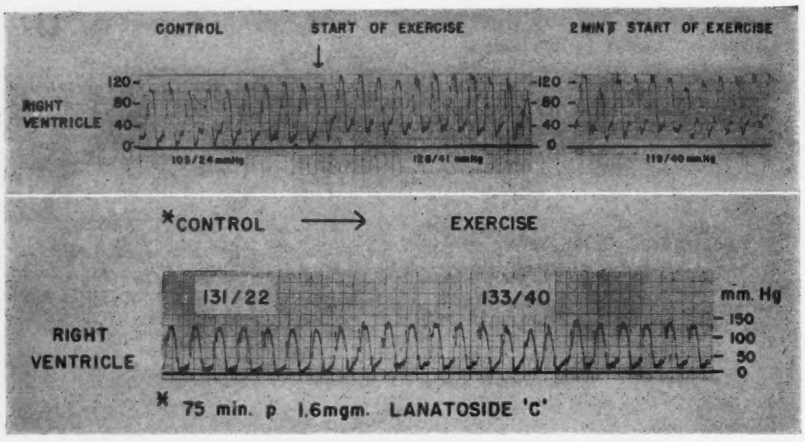


FIG. 15. Case III, M. K. (July 25, 1950.) Effect of exercise on right ventricular pressures; (A) before lanatoside C; (B) seventy-five minutes after the intravenous administration of 1.6 mg. of lanatoside C. There may be a slight error in the pressure tracings during exercise because of possible artifacts introduced during vigorous physical exertion.

by exertion or sudden movements, especially if associated with emotional tension. In M. K. the syncope was preceded by a feeling of weakness while in G. N. the syncope was preceded by marked pressure under the lower part of her sternum. Syncope is not generally associated with secondary pulmonary hypertension.

The mechanism for syncope in primary pulmonary hypertension has not been established. Our patients did not have sensitive carotid sinus reflexes. Arterial anoxemia was not observed with exercise and therefore can be eliminated as a possible cause for exertional syncope. M. K., who had numerous syncopal episodes, was exercised in the supine position during right heart catheterization,* both prior to digitalization and seventy-five minutes after the intravenous administration of 1.6 mg. of lanatoside C. Syncope was not precipitated. During exercise at both times the right ventricular end diastolic pressure increased considerably above the control values as seen in Figures 15A and B, while the peripheral pressure remained essentially unchanged. What effect changing intrapleural pressure during exercise had on the right ventricular end diastolic pressure cannot be stated since the intrapleural pressure was not measured. A grunting type of respiration was not observed during exercise. One can but speculate whether additional exercise would have precipitated a further rise in the right ventricular end diastolic pressure and acute right heart insufficiency with resultant inadequate filling of the left ventricle.

Since, as is well known, coronary blood flow is greatest during diastole, it is possible that the marked rise observed in right ventricular end diastolic pressure might impede the coronary circulation. This could account for the symptom of angina and could precipitate ventricular fibrillation or cardiac standstill[41] with resultant syncope. Although hemodynamic studies were not performed, Brill and Krygier[18] suggested that relative coronary insufficiency accounted for the chest pain and was the cause of death in those patients with this syndrome who died suddenly with but slight evidence of congestive heart failure. Diminished coronary flow might explain the sequence of events in patient G. N. who had a syncopal attack while performing a standard step-up exercise test[34] during pulmonary function studies. She first experienced excruciating substernal pain which made her stop exercising. About thirty seconds later she became unconscious, apneic, pulseless and finally cyanotic. No heart sounds were audible for the next two and one-half minutes during which time artificial respiration and oxygen were given. The heart sounds, when heard again, were slow and totally irregular. Soon coupled beats were present and, after several minutes, a regular sinus rhythm was established. On another occasion an exercise tolerance test in G. N., with electrocardiographic studies, showed depression of S-T segments in leads I and II and further downward displacement of the S-T segment in

* Studies obtained during first cardiac catheterization, July 25, 1950.

lead V_3. (Fig. 16.) Exercise was stopped with the onset of chest pain.

In addition to our cases G. N. and M. K., angina was present in 23 per cent of the cases reviewed in the literature. Brenner's case,[13] an eleven year old boy, died during an attack of chest pain. Killingsworth[15] reported the case of a ten year old boy who died following an episode of severe epigastric pain radiating to the arms. In neither these nor the remainder of the thirty-nine cases accepted as instances of primary pulmonary hypertension was coronary sclerosis or pulmonary embolism described at autopsy.

Angina and syncope have been reported in approximately 20 per cent of the cases reviewed. These symptoms may occur together or separately. It is of interest that angina and syncope do not occur in secondary pulmonary hypertension. An increased pulmonary artery pressure and right ventricular hypertrophy are common denominators in both primary and secondary pulmonary hypertension. The apparently unique effect of priscoline* (2-benzyl-4,5-imidazoline hydrochloride), a sympatholytic and adrenolytic agent,[42] in reducing the elevated pulmonary artery pressure with a concomitant increase of blood flow in primary pulmonary hypertension, suggests that an overactive autonomic nervous system may play a role in this disorder. Whether there is any direct association between this autonomic imbalance and the distinctive symptoms of angina and syncope is a matter for further investigation. Indeed, the mechanism for the production of angina and syncope based on our limited observations is probably more complex than suggested.

In only 8 per cent of the cases reviewed was hemoptysis noted. Evidence of pulmonary infarction was not found at postmortem. Orthopnea, noted in only 10 per cent of the cases, cannot be ascribed to pulmonary congestion in view of the physical, radiologic and postmortem findings. The lungs at necropsy were described grossly as well aerated except for occasional basal congestion. Microscopic studies in these cases revealed normal alveolar membranes and capillaries.

Roentgenograms of the chest should suggest the diagnosis. The characteristic x-ray findings are (1) right ventricular hypertrophy, (2) a bulging pulmonary artery segment, (3) prominent hilar vessels and (4) normal or decreased intrapulmonary vascular markings. There may be overlapping of the spine by the cardiac silhouette in the left anterior oblique view. This finding was present in two of our patients. (Fig. 4c and 10c.) In M. R. the left ventricle was normal in size at necropsy. Pulmonic stenosis[43] and idiopathic dilatation of the pulmonary artery[44] may present similar x-ray features but can be differentiated definitively from primary pulmonary hypertension by right heart catheterization. Patients with pulmonic stenosis rarely have syncopal episodes[26] and may be cyanotic when there is an associated patent foramen ovale.[39] Physical examination in these patients always reveals a loud systolic murmur, occasionally associated with a thrill over the pulmonic area, and the pulmonic second sound is frequently diminished in intensity rather than accentuated. The pulmonic second sound may be accentuated in patients with idiopathic dilatation of the pulmonary artery. However, these patients are generally asymptomatic and the electrocardiogram is usually normal.

The pulmonary hypertension in the three patients herein reported appears to originate proximal to the capillary bed. Arterial blood oxygen unsaturation is associated with pulmonary hypertension secondary to extensive capillary fibrosis. Arterial unsaturation was not

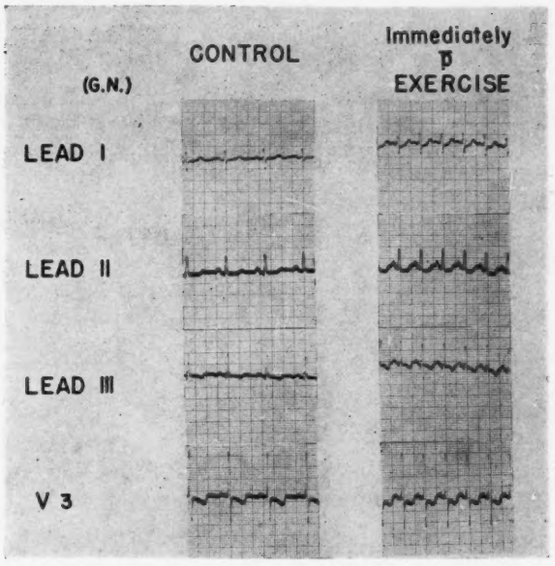


FIG. 16. Case I, G. N. Immediately following exercise there is depression of the S-T segments in leads I and II and further downward displacement of the S-T segment in V_3. The patient complained of substernal pressure at this time.

* Priscoline was generously supplied by Ciba Pharmaceutical Products, Inc., through Dr. Jock L. Graeme.

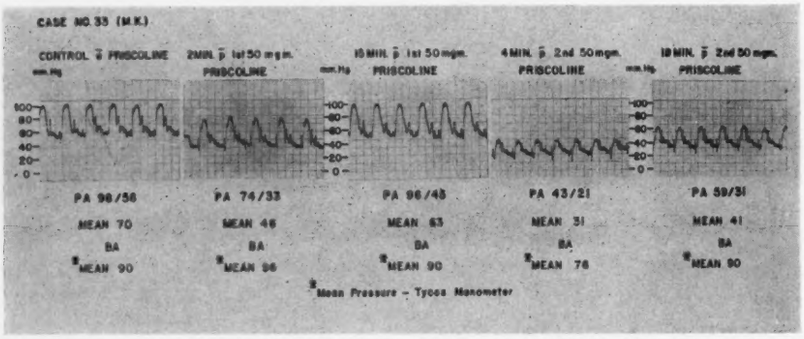


FIG. 17. Case III, M. K. There is a striking fall in the pulmonary artery pressure after parenteral priscoline, most marked after the second dose. Second dose of priscoline was administered eighteen minutes after the first dose.

observed in our patients. Necropsy in M. R. showed no changes in the pulmonary capillary bed. Furthermore, the ability simultaneously to lower the blood pressure in the lesser circulation (Fig. 17) and increase the blood flow significantly with priscoline is further evidence for a precapillary etiology of the observed hypertension. In the absence of clinical and laboratory evidence of left heart failure it would seem unlikely that the effects of priscoline on the pulmonary circulation could be ascribed to better emptying of the left ventricle. These studies are the subject of a separate report.[45] An attempt to measure capillary pressure was made in M. R. according to the method of Hellems et al.[46] Although our value was in the high normal range, 13 mm. Hg, due to our inability to withdraw blood through the catheter at the site of this pressure measurement, this result cannot be unequivocally accepted.

Intrinsic lung disease is unlikely in view of the pulmonary function and arterial blood oxygen studies as noted in Table III. The decreased ventilatory capacity in G. N. was probably the result of weakness and chest pain caused by the exertion of the test. However, these studies do reveal a significant abnormality in the ratio of oxygen consumption to ventilation during exercise. There was no increase in this ratio as normally expected.[34] This phenomenon is associated with diminished pulmonary blood flow as seen in patients with heart failure[47] and certain types of congenital heart disease.[48–50]

The results of the hemodynamic studies, namely, the high right ventricular end diastolic pressures, the increased arteriovenous oxygen differences and the low cardiac indices, place these patients in the "low output failure" category. Although there is some correlation between the hemodynamic measurements and the clinical status of the patients, it is of interest that none of them had dependent edema at the time of the studies and one of them, G. N., had no clinical signs of right heart failure.

The presence of normal blood volumes in M. K. and G. N., patients with hemodynamic evidence of right heart failure, is unusual since increased blood volumes ordinarily are associated with right heart failure.[51–53] M. K. had an enlarged, firm liver when the hemodynamic observations were made but there was no dependent edema. G. N. had no edema or enlargement of the liver.

Digitalis did not appear to influence the course of the heart failure in most of the cases reported in the literature that we considered to be instances of primary pulmonary hypertension. The hemodynamic effects of acute and chronic digitalization in M. K. and G. N. confirm this clinical impression. A detailed report of these studies will be made.[54]

The increase in systemic resistance (Fig. 12) in our patients is probably a compensatory mechanism to maintain effective systemic blood pressure in the presence of a decreased cardiac output.[55] However, the magnitude of increase in the pulmonary resistance in these patients is much greater than can be explained by the diminished cardiac output. It is postulated that the pulmonary capillary pressure is not elevated in patients with primary pulmonary hypertension. The necropsy findings of a normal sized left atrium in our case and in those reported support this idea. Therefore, it is believed that the failure to correct for pulmonary capillary pressure in calculating these resistances would not significantly alter the results.

Anoxia, known to increase the pulmonary

resistance in man in acute studies,[56] is not a factor here as demonstrated by blood oxygen studies. Cournand[32] in his latest review of the dynamics of the lesser circulation stated that there was little conclusive evidence for vasomotor control of the pulmonary circulation in normal man. That the autonomic nervous system may be a factor in primary pulmonary hypertension is suggested by the lowering of pulmonary bed resistance in the two patients with this disease who were given priscoline in an acute study.[45] In one patient the fall in resistance was much greater in the pulmonic than in the systemic circulation, whereas tetraethylammonium chloride, an autonomic blocking agent, had a greater effect on the systemic resistance in this patient.[45] (Fig. 18.) Friske et al.[57] demonstrated a relatively greater fall in the pulmonary resistance using tetraethylammonium chloride in patients with essential hypertension and normal pulmonary pressures. In reviewing the study of Fowler et al.[58] it is noted that tetraethylammonium chloride had a similar effect in some patients with secondary pulmonary hypertension. That other factors may be responsible for increasing the pulmonary artery resistance in man is further suggested by a preliminary observation showing a lack of effect of priscoline on anoxia-induced pulmonary hypertension in man.[59]

Without attempting to draw any conclusions, one is tempted to note, as has previously been pointed out,[18,20] certain similarities between essential systemic hypertension and primary pulmonary hypertension. In both conditions the etiology is unknown. The elevated blood pressure in essential systemic hypertension is considered to indicate a state of increased tonus of the pre-capillary arterioles while in primary pulmonary hypertension there would seem to be a state of increased tonus of the small pulmonary arteries. Usually there is ventricular hypertrophy of the particular circuit involved. The respective vascular beds, pulmonary or peripheral, show similar histologic patterns ranging from normal vessels to obliterative arteriolarsclerosis. In either disease hypertension may exist without significant arteriolar changes.[22,61,62] Pharmacodynamic studies[45,63] in both diseases suggest that the autonomic nervous system may be a factor in increasing the peripheral vascular resistance.

Of a group of autopsied cases reviewed by Greene et al. and cited as idiopathic dilatation of the pulmonary artery,[44] but in which heart catheterization was not done, four showed right ventricular hypertrophy without pulmonary vascular sclerosis. Two of the latter died in congestive heart failure. It may be that these cases as well as those reported by De Navasquez et al.[17] were instances of primary pulmonary hypertension.

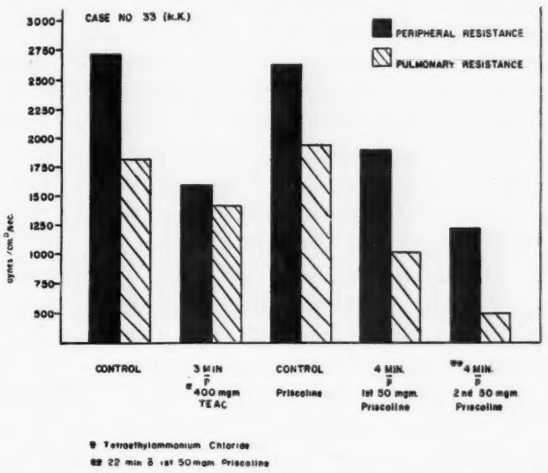


FIG. 18. Case III, M. K. The predominant effect of TEAC was on the peripheral resistance whereas priscoline exerted a maximal effect on the pulmonary resistance.

Thrombosis of the smallest vessels of the pulmonary circuit has been described in the entity under discussion and was found in the autopsied cases in this series. Rich[60] described similar lesions in 90 per cent of cases of tetralogy of Fallot that he studied. He believed that the predisposing factors for the development of thrombosis were polycythemia and sluggish pulmonary blood flow. The data which we have presented show that patients with primary pulmonary hypertension have a decreased pulmonary blood flow without polycythemia. There may be other predisposing factors in the pulmonary vascular bed in this disease to account for this unusual finding not described in other conditions with diminished pulmonary blood flow. In view of the preponderance of the sclerotic changes over the number of thrombotic lesions in the autopsied case reported it seems unlikely that sclerosis was the result of thrombosis.

Since it is generally accepted that the hallmark of prolonged hypertension of the greater circulation, essential or secondary, is found in the arteriolar bed, many of the observed changes in the pulmonary vasculature in primary pulmonary hypertension are similarly interpreted.

Undoubtedly, these sclerotic vessels add a significant increment to an already excessive vascular resistance further burdening the right heart but the deduction that these changes initiate the hypertension seems unwarranted. The findings of a normal pulmonary arteriolar bed in several cases of isolated right ventricular hypertrophy,[6,12,14,16,17,20,22] assumed by us to be instances of primary pulmonary hypertension, one proven to have marked pulmonary hypertension by right heart catheterization[22] and the effect of certain drugs in lowering the pulmonary resistance, suggest that the sclerotic changes, when seen, are of a secondary nature. Conceivably, involvement of the pulmonary vasculature by pulmonary emboli, parasitic infestations, lymphangitic carcinomatosis or pulmonary arteritis, if sufficiently severe and diffuse, might produce an identical clinical picture.

The material herewith presented indicates that primary pulmonary hypertension is a formidable disease with a grave prognosis. Heart catheterization not only enables the clinical investigator to make this diagnosis during life but also permits him to evaluate quantitatively the effects of various therapeutic measures and to obtain some additional information about the dynamics of the pulmonary circulation. The clinician is often faced with the problem of treating the effects of a disease while the etiology is still obscure. A logical approach to therapy in primary pulmonary hypertension would be to relieve the markedly increased resistance in the pulmonary circulation. Priscoline administered parenterally in acute studies has proven effective in this regard.[45] In addition, clinical improvement as manifested by increased exercise tolerance has also been noted after parenteral priscoline. However, studies thus far would indicate that the beneficial effects in primary pulmonary hypertension of parenterally administered priscoline are of short duration, i.e., twenty to thirty minutes; the response to chronic oral priscoline is inconclusive. A similar approach might be indicated in certain cases of pulmonary embolism with occlusion of but a relatively small segment of the pulmonary arterial tree. In view of the known reserve of the pulmonary circulation the pathologic findings in such cases seem inadequate to explain the fatal outcome. It is possible that reflex sympathetic overactivity might add a significant increment to the pulmonary resistance, sufficient to cause acute cor pulmonale and death. Priscoline or similarly acting drugs would then seem indicated in this situation. However, the conclusions drawn by various investigators in evaluating the role of vasomotor activity in induced pulmonary embolization in animals are contradictory.[64–67] Studies of a similar nature are in progress in this laboratory.

Since primary pulmonary hypertension presents certain unique features pointing toward isolated sympathetic overactivity, surgical thoracic sympathectomy must be considered. This, of course, is a subject for further investigation.

SUMMARY

The concept of primary pulmonary hypertension is defined and the clinical and hemodynamic features in three patients with this disease are presented. Such cases present a clinical syndrome that has been previously described under various names, e.g., "primary pulmonary vascular sclerosis," "right ventricular hypertrophy of obscure origin" and "idiopathic pulmonary hypertension."

The salient clinical features in this syndrome are exertional weakness and dyspnea in patients who subsequently develop right heart failure without antecedent cardiac or pulmonary disease. Effort syncope and angina are most significant when present. Sudden death is not infrequent. The pertinent physical findings are a normal systemic blood pressure, clear lungs, an accentuated pulmonic second sound and the variability or absence of heart murmurs. Venous distention and hepatomegaly occur unassociated with peripheral edema or ascites except late in the course of the disease. Cyanosis, when encountered, is a terminal feature unless the disease is complicated by a patent foramen ovale. This syndrome has been seen in both sexes at all ages but is most common between the ages of twenty and forty years.

The electrocardiographic tracings are consistent with right ventricular hypertrophy. The characteristic x-ray findings are (1) right ventricular enlargement, (2) a bulging pulmonary artery segment, (3) prominent hilar vessels and (4) normal or diminished intrapulmonary vascular markings.

Marked right ventricular hypertrophy is a constant pathologic finding in primary pulmonary hypertension but the nature, severity and distribution of the pulmonary vascular changes proximal to the capillary bed show considerable

variation. In some cases no significant pulmonary vascular changes are noted.

Pulmonary function studies were performed in two of the patients and ruled out intrinsic lung disease. Hemodynamic studies, utilizing the technic of right heart catheterization, were performed in the three patients presented in this series. All had greatly elevated pulmonary artery pressures, elevated right ventricular end diastolic pressures, diminished cardiac outputs, increased arteriovenous oxygen differences and normal arterial blood oxygen saturations. The blood volumes and hematocrits were normal in two of the patients and slightly elevated in the third. One patient had no clinical evidence of right heart failure and none had edema.

An attempt was made to correlate the hemodynamics at rest and during exercise with some of the clinical findings. A seven- to ninefold increase in pulmonary resistance was calculated at rest. Physiologic studies and postmortem findings were presented to support the view that the locus of the increased resistance is in the small pulmonary arteries.

Isolated overactivity of the sympathetic nervous system was suggested by the pronounced effect of priscoline, an adrenolytic and sympatholytic agent, in lowering the pulmonary artery blood pressure. On the basis of the material presented the problem of sympathectomy in primary pulmonary hypertension was raised.

Acknowledgments: The authors wish to express their appreciation to Drs. Dickinson W. Richards, Jr., André Cournand and David Seegal for reviewing this paper and for their valuable suggestions concerning the material presented. Technical assistance by Miss Leila Israel and Mrs. Dorothy Bowen is gratefully acknowledged.

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Pulmonary Function Studies in Polycythemia Vera*

Results in Five Probable Cases

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THERE have been numerous studies of pulmonary function in polycythemia vera. The results have been variable and inconsistent and many of the older technics which were used are open to criticism at the present time. Therefore, the results of previous investigators measuring cardiac output and arteriovenous oxygen differences will not be listed. Of particular interest are reported results of vital capacity, residual air, total capacity, ratio of residual air to total capacity, and arterial oxygen saturation at rest and exercise. (Table I.)

TABLE I
RESUME OF RESULTS REPORTED IN THE LITERATURE

	Vital Capacity
Isaacs[1]	Decreased, 1 case; average vital capacity 2115; predicted value 4700; average % predicted value 45 %
Brooks[2]	Decreased, 1* case; vital capacity 1.88 L. before treatment; after treatment 2.36 L. (phenylhydrazine)
Altschule[3]	3 cases, normal in 2; slightly decreased in 1; no change in 2 cases treated with phlebotomy
Stewart[4]	6 cases, reduced in 3; one case treated; vital capacity 3.3 L. before treatment to 3.9 L. after treatment
	Residual Air
Harrop[5]	Increased, 7 cases
Brooks[2]	Increased, 1* case; residual air 1.19 L. before treatment; after treatment 0.99 L.
	Total Capacity
Harrop[5]	Normal, 7 cases
Brooks[2]	Decreased, 1* case; 3.07 L. before treatment; 3.35 L. after treatment
	Ratio of Residual Air to Total Capacity
Harrop[5]	Increased, 7 cases
Brooks[2]	Increased, 1* case; before treatment 38.7 %; after treatment 29.5%
	Arterial O_2 Saturation at Rest
Harrop[5]	Decreased
Wasserman[6]	17 cases with arterial O_2 saturation determinations; 8 below range 94% to 98% and one case showed 88.2% saturation
von Bergmann,[7] Brooks,[2] Hitzenberger,[8] and Rover[9]	Normal
	Arterial O_2 Saturation After Exercise
Harrop[5]	3 cases; 91%→89%; 93%→87%; 95%—90%

*Second case reported was secondary polycythemia.

Examination of this table would indicate that in general the vital capacity is reduced, residual air increased, total capacity normal or decreased and ratio of residual air to total capacity is increased. The arterial oxygen saturation is normal or slightly reduced at rest and decreased with exercise. In Brooks' case[2] the lung volumes after treatment improved. Other investigators found an increase in blood volume[10] and viscosity[1] in polycythemia.

We have made detailed studies of pulmonary function in five cases of polycythemia. All of these were studied before and after treatment with phlebotomy.

METHODS

The measurement of residual air volume was made using an open circuit method in which the nitrogen of the lungs is washed out by continuous inhalation of pure oxygen and collected over a period of seven minutes. An index of intrapulmonary mixing was obtained by sampling of the alveolar air at the end of this period.[11]

The measurements of lung volumes and maximum breathing capacity were obtained using the spirographic technic.[11]

Arterial blood samples were obtained from the brachial artery using an indwelling Cournand-

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type needle. The blood was collected by the technic described by Riley,[12] using heparin to prevent clotting and a small globule of mercury in the syringe to facilitate mixing. The oxygen content and capacity and the carbon dioxide content were determined on duplicate samples of Riley.[12] Duplicate measurements were made using two Roughton-Scholander syringes and all samples checked within 2 mm. of mercury. Expired air samples were collected in duplicate simultaneously with the blood specimens. Oxygen intake and carbon dioxide output were

TABLE II A

PULMONARY FUNCTION STUDIES BEFORE AND AFTER PHLEBOTOMIES IN FIVE CASES OF POLYCYTHEMIA VERA

	Case I (2.85 L. in 21 days)		Case II (2.5 L. in 21 days)		Case III (3.7 L. in 30 days)		Case IV (5.4 L. in 32 days)		Case V (4.8 L. in 60 days)	
	Before	After	Before	After	Before	After	Before	After	Before	After
Red blood count, million per cu. mm.	7.4	4.8	6.8	4.8	7.7	4.7	7.5	4.96	7.25	5.2
Hemoglobin, gm. per 100 cc.	22	14.6	20.1	14.5	23.6	15	23	15.7	21.8	16.3
Hematocrit, %	67	46	54	47	73	46	67	43	77	48
Blood volume cc.; P^{32} Actual / Predicted	10.000 / 3960	7500 / 3960	6300 / 4800	5750 / 4800	7930 / 3890	5360 / 3890	----	----	8450 / 5020	7900 / 5020
Vital capacity in cc. Actual / Predicted	4130 / 4130	4430 / 4130	4540 / 4660	4525 / 4660	3838 / 4180	3780 / 4180	2070 / 4070	3930 / 4070	2950 / 4940	4500 / 4940
Residual air cc. Actual / Predicted	1430 / 1320	1582 / 1320	1286 / 1150	1005 / 1150	1144 / 1030	863 / 1030	1626 / 1320	1700 / 1320	1378 / 1220	1307 / 1220
Total capacity in cc. Actual / Predicted	6040 / 5450	6292 / 5450	6071 / 5810	5627 / 5810	4807 / 5210	4530 / 5210	3937 / 5390	5970 / 5390	4435 / 6160	5926 / 6160
Residual air / Total capacity X 100 Actual / Predicted	23.7 / 24.4	25.2 / 24.4	21.2 / 19.8	17.9 / 19.8	23.8 / 19.8	19.1 / 19.8	41.4 / 24.4	28.5 / 24.4	31.1 / 19.8	22.1 / 19.8
Alveolar N_2, (normal 2.5 %)	1.6	2.02	2.18	1.7	1.54	1.26	2.5	2.02	1.88	1.53
Maximum breathing capacity (% of normal)	93.5	102.0	70.3	103	133	173	48.8	95.3	33.3	60.5
Maximum breathing capacity L./min. Actual / Predicted	92.0 / 98.4	124.5 / 98.4	111 / 158	163 / 158	157 / 118	204 / 118	62 / 127	121 / 127	55 / 164	99 / 164
Arterial O_2 saturation (normal 94–98 %)	94.4	95.0	95.5	97.0	95.4	95.8	69	95.4	65	80.3
Arterial pO_2 mm. Hg (normal 95 mm. Hg)	87	92	89	101	104	92	34	92	38	51
Arterial pCO_2 mm. Hg (normal 40 mm. Hg)	43	43	47	40	45	47	78	43	73	66
Arterial CO_2 content (normal 44–53 vol. %)	41.3	50.3	44.7	47.7	43.4	52.4	63.1	51.8	59.3	60.4
pH (calculated) (normal 7.4)	7.35	7.39	7.33	7.42	7.38	7.38	7.3	7.42	7.28	7.34
Ventilation L./min./M^2 At rest Normal 3.20 ± .65	4.68	4.39	3.58	3.61	3.57	3.64	3.01	3.64	3.31	3.20
After exercise Normal 8.70 ± .81	10.8	13.6	12.5	9.56	4.33	9.05	----	9.35	9.48	9.56
Oxygen consumption in cc./min./M^2 At rest Normal 129 ± 13	152	154	180	163	150	137	144	140	166	124
After exercise Normal 480 ± 74	522	602	775	634	318	486	----	443	454	458
Oxygen removal in cc./L. of ventilation At rest Normal 46.8 ± 7.1	38.9	42.3	61.0	54.5	51.7	46.2	58.2	46.5	61.8	52.0
After exercise Normal 54.8 ± 6.2	57.6	53.1	74.7	79.9	90.4	65.7	----	56.8	58.4	58.1
Arterial O_2 saturation after exercise (normal 94–98 %)	94.4	94.0	98.0	96.0	75.0	95.0	----	93.7	60.6	78.6

using the Van Slyke-Neill apparatus.[13] All samples checked within 0.2 volumes per cent.

The arterial blood tensions of oxygen and of carbon dioxide were determined directly in millimeters of mercury, using the direct method calculated from the percentage of oxygen and carbon dioxide found in these expired air samples, as determined in a Scholander gas analyzer.[14] The duplicate measurements checked within 0.04 per cent.

Arterial blood samples and expired air were collected under basal conditions with the patients breathing room air, high and low oxygen concentrations each for twenty-minute periods when indicated. Finally oxygen saturation was determined after one minute of standard exercise and the expired gas during the exercise was collected in a Douglas bag and analyzed. During the five-minute recovery period the expired air was collected and analyzed. The expired air, except during exercise, was collected in the Tissot apparatus and the spirogram attached permitted calculation of the respiratory rate and tidal air under the various conditions. The alveolar-arterial gradients were calculated from the data obtained according to the method of Riley and Cournand.[15]

pH determinations were calculated from line charts of the Henderson-Hasselbalch equation.[16]

The blood volumes were determined by the use of P^{32} labeled red cells.

TABLE II B

PULMONARY FUNCTION STUDIES BEFORE AND AFTER PHLEBOTOMIES IN FIVE CASES OF POLYCYTHEMIA VERA

		Case I (2.85 L. in 21 days)		Case II (2.5 L. in 21 days)		Case III (3.7 L. in 30 days)		Case IV (5.4 L. in 32 days)		Case V (4.8 L. in 60 days)	
		Before	After	Before	After	Before	After	Before	After	Before	After
Room air breathing	Alveolar pO_2 mm. Hg	100	101	88	100	92	91	48	92	58	69
	Arterial pO_2 mm. Hg	87	92	89	101	104	92	34	92	38	54
	Arterial pCO_2 mm. Hg	43	43	47	40	45	47	78	43	73	58
	Alveolar-arterial gradient	13	9	-1	-1	-12	-1	14	0	20	15
	Dead space ml. % of tidal air	35	31	24	18	22	31	42	31	27	31
High oxygen breathing	Alveolar pO_2							257*		97†	288*
	Arterial pO_2							95		54	91
	Arterial pCO_2							84		69	64
	Alveolar-arterial gradient							162		43	197
	Dead space							48		27	31
Low oxygen breathing (12.4%)	Alveolar pO_2	47	42	41	47	37	43				
	Arterial pO_2	44	38	40	52	37	35				
	Arterial pCO_2	38	41	41	36	46	42				
	Alveolar-arterial gradient	3	4	1	-5	0	8				
	Dead space	28	31	22	19	32	31				

*51.7 %
†27.35 %

COMMENTS

Five cases of polycythemia vera were subjected to detailed pulmonary function studies before and after phlebotomies. The results of these studies are listed in Table II.

A basic change in all five cases was an increase in the maximum breathing capacity after phlebotomy. This is believed to be due to an increase in the elasticity and a decrease in the viscous resistance of the lung tissue to changes in shape, and when present, to a decrease in the anoxemia. These former changes are probably due primarily to a decrease in the blood viscosity and to some extent a decrease in total blood volume. This increase in maximum breathing capacity was the only change noted in Cases I and II.

Case III, in addition to the maximum breathing capacity change, demonstrated an unusual aberration of pulmonary function. During exercise there was a failure to increase ventilation significantly, the actual value being approximately half the predicted value. This in turn was reflected by an inadequate oxygen consumption during exercise and consequently a decrease in oxygen saturation with exercise. This phenomenon is especially interesting in view of the fact that the patient had the ability to hyperventilate, considering that the maximum breathing capacity was 133 per cent of the predicted normal. He also had the stimuli to hyperventilate with exercise, viz., low pH, high arterial pCO_2 and anoxia. However, there was marked hypoventilation. In view of these facts we feel justified in concluding that this patient's respiratory center was insensitive to these stimuli. Since this patient did manual labor, it is reasonable to assume that he was anoxic during most of his working day. This was substantiated by the fatigue, of which the patient was aware. Following phlebotomies this patient's ventilation and oxygen consumption during exercise and his oxygen saturation after exercise returned to normal. However, his effective alveolar ventilation at rest, as reflected by the arterial pCO_2, remained elevated. These

changes with phlebotomy would suggest that the respiratory center damage was at least partially reversible.

Case IV demonstrated a marked decrease in vital capacity, total capacity and maximum breathing capacity. The mechanisms for these changes are believed to be the same as postulated before, namely, increased blood viscosity and volume causing a decrease in elasticity, and an increase in the viscous resistance of the lung tissue. Before phlebotomy this patient had a definite distribution gradient indicating perfusion of poorly ventilated areas.[15,18] One explanation for this phenomenon is that in the normal individual at rest all the alveoli are not being well ventilated or perfused. In this patient with polycythemia and increased blood volume there was an opening up of the capillary beds of some of these poorly ventilated alveoli. This would result in a poor correlation of perfusion and ventilation and thus give rise to a high distribution gradient. A similar mechanism has been postulated by Riley in patients with mitral stenosis and pulmonary hypertension.[19] This patient was strikingly unsaturated at rest, with a very poor effective alveolar ventilation in view of the arterial pCO_2 of 78 mm. of mercury. Thus there appear to be two factors contributing to the arterial oxygen unsaturation at rest, namely, inadequate ventilation and venous admixture. In addition, we believe that a third factor was playing a part, namely, respiratory center damage. This is substantiated by the fact that this patient had the ability to ventilate 62 L. per minute, at least for short periods of time. He certainly had stimuli for hyperventilation at rest with an arterial pH of 7.3, arterial pCO_2 of 78 mm. of mercury and arterial pO_2 of 34 mm. of mercury. Despite these strong stimuli this patient's ventilation at rest, while breathing room air, was only 7.83 L. per mm., 13 per cent of his maximum breathing capacity.

One of the remarkable features of this case was the complete return to essentially normal values for ventilation and gas exchange following adequate phlebotomy. This again would indicate the reversibility of the lung volume changes, the distribution gradient and the respiratory center damage.

We do not believe that these changes were due to any significant underlying chronic pulmonary disease such as emphysema since the alveolar nitrogen after breathing pure oxygen was normal and the spirogram showed no evidence of obstruction. Furthermore, except for a slight increase of the residual air, the lung volume and arterial gas studies all became normal after phlebotomy. This would seem to preclude the presence of any significant pulmonary parenchymal disease. It is of interest to note that the alveolar nitrogen was within normal limits before and after phlebotomy even though tension studies indicated a high venous admixture component. This is in striking contrast to the findings in pulmonary emphysema in which a high alveolar-arterial gradient exists with high oxygen and a high alveolar nitrogen after breathing pure oxygen for seven minutes. Evidently, when there are permanent intrinsic tissue changes in the lung, nitrogen is not washed out as easily as in this patient with polycythemia.

Case V demonstrated essentially the same pulmonary function abnormalities as Case IV except that in addition there was a high diffusion gradient. This possibly was due to the fact that the diffusing surface, i.e., the capillary bed, was reduced by thrombosis. Following phlebotomies this patient's lung volumes returned to normal. This is consistent with the hypothesis that these changes were due to decreased elasticity and increased viscous resistance of the lung as a result of the large volume of viscous blood these patients have. Failure of the maximum breathing capacity to return completely to normal is believed to be due to persistence of the anoxia. This would interfere with the muscular effort necessary for performing the maximum breathing capacity.

The persistence of anoxia was largely due to the continued poor correlation between ventilation and perfusion. This gas exchange abnormality was then primarily due to poor effective alveolar ventilation (arterial pCO_2 66 mm. of mercury) and less to opening up of the capillary beds of alveoli which normally are poorly ventilated. The poor effective alveolar ventilation in turn is thought to reflect respiratory center damage. At this stage the patient had a maximum breathing capacity of 99 L. per minute and was ventilating only 7.55 L. per minute despite the presence of strong stimuli. Thus he was utilizing only 7.6 per cent of his maximum breathing capacity at a time when his arterial pO_2 was 51 mm. of mercury and pCO_2 66 mm. of mercury. In order to eliminate the possibility of anoxic depression of the respiratory center the patient was placed in a Drinker respirator for forty-eight hours. With

this procedure after twenty-four hours the arterial pCO_2 dropped to 53 mm. of mercury, CO_2 content went from 62.1 volumes per cent to 51.6 volumes per cent, and the oxygen saturation rose to 93 per cent. However, one hour after removal from the respirator the arterial pCO_2 rose to 61 mm. of mercury and the oxygen saturation dropped to 82 per cent. This would seem to indicate respiratory center damage due to causes other than anoxia; however, a more prolonged period in the respirator might be necessary before this could be definitely ruled out.

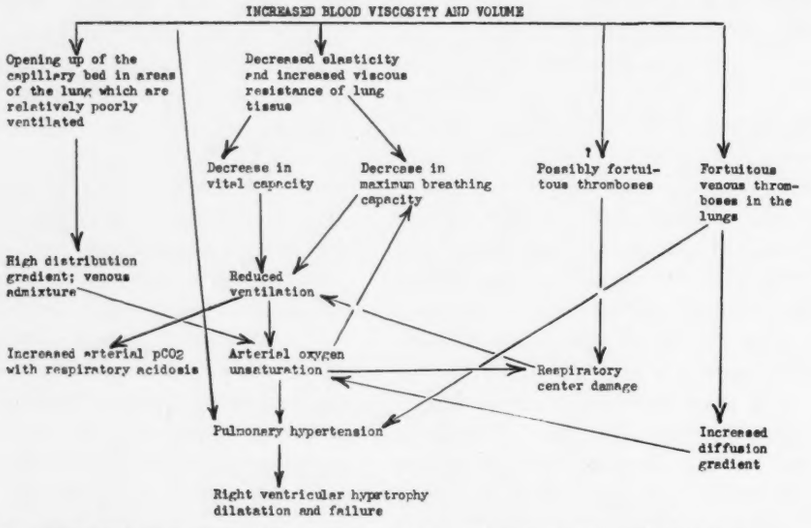

FIG. 1. Sequence of events which may occur in some cases of polycythemia vera.

We, therefore, believe that this patient demonstrates not only the possible irreversibility of respiratory center damage but also possible progression of this disease along lines not previously indicated.

OBSERVATIONS

We have presented pulmonary function studies in five patients with polycythemia vera. As a result of these studies we believe that the following sequence of events may occur in some patients with this disease. (Fig. 1.) The increased blood viscosity and volume causes a decrease in the elasticity and increase in the viscous resistance of the lungs. This in turn leads to a decrease in the maximum breathing capacity and the vital capacity. These changes result in impairment of ventilation which gives rise to a poor correlation between ventilation and perfusion and thereby creates a high distribution gradient with resultant arterial oxygen unsaturation, increased arterial pCO_2 and respiratory acidosis. This anoxia would tend to augment the decrease in maximum breathing capacity. In addition, the increased blood viscosity and volume would tend to open the capillary bed of alveoli which are normally poorly ventilated and thus increase the distribution gradient and resultant anoxia.

Since polycythemia vera predisposes to thromboses, it is not unreasonable to assume that these may occur in the alveolar capillaries and thereby give rise to a diffusion gradient which would further contribute to the anoxia. Finally, since three of our five cases demonstrated evidence of respiratory center damage, this would be another mechanism further to impair ventilation and thereby contribute to the anoxia. Undoubtedly, this respiratory center damage is in part due to anoxia. However, this would not account for all of it since Case III showed evidence of respiratory center damage while at rest when he had a high arterial pCO_2 but normal oxygen saturation, and in Case V relief of the anoxia did not improve the function of the respiratory center.

We did not take measurements of the pulmonary artery pressure. However, in view of the development of pulmonary hypertension in normal individuals breathing low oxygen tensions, as demonstrated by Motley et al.,[20] and in view of the accentuated second pulmonic sound in two of our patients (Cases III and V), it is not unreasonable to assume that these patients may go on to pulmonary hypertension and finally to right ventricular failure.

Objective analysis of our findings would admit another possibility. Cases of polycythemia vera,

as we know them now, may represent a heterogeneous group. Some of these patients may actually represent a polycythemic response to medullary center damage of unknown etiology. This could certainly be true of Cases III, IV and V if one would admit that our present technics of studying pulmonary function are not sensitive enough to discern small quantitative changes resulting from such impairment.

CASE REPORTS

CASE I. A fifty-five year old hat salesman was well until approximately four weeks before admission to the hospital. At that time he noted the gradual onset of painless gangrenous changes of the tips of the distal phalanges of the four medial fingers of the left hand. Because of these changes the patient was hospitalized.

Physical examination on admission revealed a slim, plethoric white male in no acute distress. There was injection of the conjunctivas and slight engorgement of the veins of the fundi. The lungs were clear to percussion and auscultation with normal chest expansion and diaphragmatic excursion. The heart was not enlarged to percussion and there was a regular sinus rhythm with a rate of 82. The blood pressure was 122/88 mm. of mercury in the right arm and 130/85 mm. of mercury in the left arm. A_2 equaled P_2. No murmurs were heard. The abdomen was negative except for a firm, nontender spleen palpable two fingerbreadths below the costal margin. Examination of the extremities revealed no clubbing. There was coldness and cyanosis of the distal phalanges of the four medial fingers of the left hand with approximately 5 mm. areas of almost black discoloration at the tips of these fingers.

The hemogram and related data are tabulated. Platelet count was 400,000 and the white blood count 14,700. The remainder of the laboratory findings, including chest x-ray and fluoroscopy, were within normal limits.

Following phlebotomy of 2.85 L. in twenty-one days there was marked subjective improvement and the appearance of the hands returned to normal.

This patient fulfilled all the criteria for the diagnosis of polycythemia vera. He had a polycythemia with leukocytosis, increase in platelets and splenomegaly. In addition, he presented venous thromboses, one of the frequent complications of polcythemia.

CASE II. A thirty-three year old white male had noted lethargy, irritability, frequent epistaxis and a reddish purple color of the skin for three years preceding admission. Physical examination revealed a slightly obese, well developed, young male with plethoric facies. There was no respiratory distress. The eyes showed injection of the conjunctivas and fundi revealed 1 diopter of papilledema with marked distention of the veins. The heart and lungs were within normal limits. The spleen was palpable two fingerbreadths below the costal margin. The remainder of the physical examination was non-contributory.

The hemogram and related data are tabulated. The platelet count was 280,000 and white blood count 9,600. The blood urea nitrogen, fasting blood sugar, urine and urinary 17-ketosteroid excretion were within normal limits. Blood serologic tests were negative. The electrocardiograph was normal.

X-ray examination of the chest revealed the lung fields to be clear and the heart normal in size and configuration. Fluoroscopic examination of the chest demonstrated good diaphragmatic excursion. A bone survey by x-ray was negative and did not demonstrate any osteoporosis.

Following phlebotomies, 2.5 L. in twenty-one days, the patient noted increased energy, marked decrease in his irritability and the plethora was less striking.

This patient fulfilled many of the criteria for the diagnosis of polycythemia vera. He had the typical history and facial appearance of patients with this disease. In addition there was an enlarged spleen and increase in the red blood count, platelet count and plasma volume. One of the features which was missing was the leukocytosis which 50 per cent to 70 per cent of these patients demonstrate.[17] Other causes for polycythemia were sought but none could be found.

CASE III. A thirty year old Negro male was admitted to the hospital complaining of abdominal pain of two years' duration. The pain was described as transient, moderately sharp in the right para-umbilical region radiating occasionally to the left upper quadrant. There was no relation to meals, position or bowel movements. Examination for this complaint at its onset two years before admission failed to reveal any significant pathologic disorder. Two months before admission the patient was admitted to another institution, polycythemia was discov-

ered and he was transferred to this hospital for further investigation and therapy. Past history and system review were non-contributory.

Physical examination on admission revealed a well developed and well nourished Negro male in no acute distress. There was an underlying redness in the skin but no cyanosis. The scleras were suffused. The chest revealed no bony deformity and a normal P-A diameter. Respirations were primarily diaphragmatic but with forced breathing there was adequate movement of the chest cage. The breath sounds were vesicular and there were no rhonchi or rales. Examination of the cardiovascular system was within normal limits except for an accentuated P_2. The blood pressure was 120/80. Abdominal examination revealed no pathologic findings. There was no splenomegaly.

Urine analyses, serology, stool examinations for occult blood, ova and parasites and serum protein determinations were within normal limits. Intravenous pyelogram, gastrointestinal series and barium enema were within normal limits. The hemogram and related data are tabulated. The white blood count was 9,300 with a normal differential, platelets 325,000. Sternal marrow examinations revealed essentially normal findings. Fluoroscopic examination of the chest revealed good diaphragmatic excursions, clear lung fields and a normal cardiovascular silhouette. The electrocardiogram was within normal limits and the electroencephalogram was reported as a normal record in a drowsy patient.

Pulmonary function studies were performed on admission and following phlebotomies totaling 3.7 L. in thirty days there was a striking subjective improvement with a sense of well-being and an increase in work capacity. On examination the plethora disappeared and the previously accentuated P_2 was markedly diminished. One of the striking features before phlebotomy was a failure to increase ventilation following exercise. After completion of the phlebotomies the patient demonstrated a normal ventilatory response to exercise. This point is well demonstrated quantitatively in the tabulated pulmonary function studies.

Polycythemia was noted in this young colored male as an accidental finding. Despite the absence of some of the criteria for the diagnosis of polycythemia vera, viz., splenomegaly and leukocytosis, none of the usual causes for secondary polycythemia could be found. Thus the diagnosis of polycythemia vera was made by exclusion. The cause for the patient's abdominal complaints was not apparent.

CASE IV. A fifty-four year old white male was admitted to the hospital because of somnolence which had begun four years previously and gradually increased. Prior to hospitalization he slept twenty hours out of twenty-four. He was lethargic, apathetic and his concentration was poor. During gatherings with his friends he would fall asleep. He described his speech as thick and for many months his vision was blurred. In 1920 the patient weighed 145 pounds. He progressively gained weight from this time until admission. During the year before admission he was dyspneic with effort and tired easily. There was no history of chest pain, orthopnea, or nocturnal paroxysmal dyspnea. Five years before admission he had been hospitalized at another institution and at that time his weight was 350 pounds, hemoglobin 18.5 gm. per cent, red blood count 6,500,000 and the hematocrit was 62 per cent.

On examination he was found to be an extremely obese male who was cyanotic and very lethargic. He was comfortable lying flat. The blood pressure was 145/95. There was a bilateral proptosis. The conjunctivas were markedly injected and examination of the fundi disclosed 1 diopter of papilledema with venous engorgement. The breath sounds were diminished throughout and there were a few rales at both lung bases. The heart was normal. Examination of the abdomen was impaired by the marked obesity. The genitalia were normal. There was slight pitting edema and varicosities of both legs. The skin was dusky and there were abdominal striae. There was a stasis dermatitis of the lower limbs. The remainder of the examination was normal.

The hemogram and related data are tabulated. The platelet count was 306,510, and the white blood count 6,550. Urine analysis was negative. The blood urea nitrogen was 18 mg. per cent, Mazzini test negative, fasting blood sugar 97 mg. per cent, serum cholesterol 152 mg. per cent and chlorides 90 mEq./L. The CO_2 combining power was 69 volumes per cent, serum bilirubin 1.0 mg. per cent and urinary ketosteroid excretion was normal. X-ray examination of the chest disclosed normal lung fields and cardiac silhouette. Fluoroscopy confirmed this as well as demonstrating the presence of good diaphragmatic motion. X-ray of the

thoracic and lumbar spine showed marked hypertrophic arthritis. The sella turcica was normal. The electrocardiograph showed a sinus arrhythmia with frequent supraventricular premature contractions.

The patient was initially digitalized because of presumed cardiac failure. However, after a red blood count and hemoglobin were obtained, digitalis was discontinued. Repeated phlebotomies totaling 5.4 L. in thirty-two days were performed with marked subjective and objective improvement. His lethargy lessened considerably. He became much more active and alert. His hours of sleep decreased from approximately twenty hours a day to eight. Electroencephalograms were obtained, one early during the patient's hospitalization and one after treatment. The initial record disclosed evidence of focal vascular lesions. The follow-up electroencephalograph was mildly abnormal due to scattered slow waves in the occipital and central areas but showed a definite improvement.

The history and physical findings of this patient were consistent with progressive polycythemia and obesity. The spleen was not palpable but this examination was impaired by his pendulous abdomen. The hematocrit, hemoglobin and red blood count were high. The blood volume was not determined because of technical difficulties. It was thought that this patient probably represented a case of polycythemia vera although there was no leukocytosis and the presence or absence of splenomegaly could not be ascertained.

Case v. A thirty-two year old male was first admitted in April, 1948, complaining of fatigue and lassitude. At that time the history revealed that in 1943, while in the army, the patient noted reddish blue discoloration of the face. He was hospitalized in an army hospital in which red blood counts of eight to nine million were recorded and the patient was given a medical discharge in 1945 with a diagnosis of polycythemia vera. During his first admission to the hospital he was studied for possible Cushing's syndrome, brain tumor, congenital heart disease and pulmonary disease with negative results. Two arterial oxygen saturation tests at rest done at that time showed 96 per cent saturation. The final discharge diagnosis was polycythemia vera. The patient was readmitted in June, 1950, because of increasing discoloration of the face and an incapacitating degree of lethargy.

On examination the patient was moderately obese and cyanotic but was in no respiratory distress. The fundi showed distended, tortuous veins and blurring of the disc margins. The chest was thick and obese with good mobility and examination of the lungs disclosed a few basilar fine moist rales bilaterally. The area of cardiac dullness was not percussible, the rhythm was regular, P_2 was markedly accentuated and there were no murmurs. The abdomen was obese and no organs or masses could be felt.

The hemogram and related data are tabulated. The white blood cell and platelet counts ranged about 7,000 and 200,000, respectively. Blood serologic tests were negative. The urine contained negative to 2 plus protein with occasional hyaline and granular casts. A glucose tolerance test and 17-ketosteroid excretion were normal. The blood sodium, blood urea nitrogen and serum proteins were within normal limits. A bone survey by x-ray failed to demonstrate any osseous abnormalities. The chest x-ray revealed normal lung fields and cardiovascular silhouette. Fluoroscopy demonstrated good diaphragmatic excursion. An electrocardiogram showed non-specific T wave changes. The venous pressure was 115 mm. of H_2O and circulation time arm to tongue, using decholin, was fourteen seconds.

The hospital course was uneventful. Following phlebotomy, of 4.8 L. in sixty days, there was a moderate but not striking decrease in the patient's symptomatology.

This patient represented the most complicated case which was studied. Here again, polycythemia vera was diagnosed by exclusion since the patient never demonstrated leukocytosis or thrombocytosis and the obesity precluded adequate examination for splenomegaly. In addition, before phlebotomy, although the red blood cell mass was increased the plasma volume was decreased. In view of the work of Berlin et al.[10] the values for plasma volume cannot be used for differentiating primary from secondary polycythemia. An adequate explanation for the polycythemia could not be found and in view of the normal oxygen saturation three years before the present admission at a time when the patient was polycythemic, we felt justified in considering him a case of polycythemia vera.

SUMMARY

Detailed pulmonary function studies are reported in five cases of polycythemia, probably

polycythemia vera. The results would indicate that some of these patients may show incapacitating changes in directions not previously indicated. Thus definite changes in ventilation and gas exchange may occur, with the development of severe degrees of anoxia. The anoxia and other unknown factors result in respiratory center damage and a vicious cycle may be initiated. Since these changes were not reversible in all our cases, early and adequate therapy would seem to be imperative in patients with polycythemia vera.

The possibility is pointed out that polycythemia vera may be a heterogeneous disease with some of the cases representing a polycythemic response to primary respiratory center damage of undetermined etiology.

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Effect of Cortisone and ACTH on Fluid and Electrolyte Distribution in Man*

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PREVIOUS evidence indicates that the adrenal hormones may influence the distribution of fluid between cells and the extracellular compartment.[1–8] It is not clear whether this redistribution is limited to water and is achieved solely by a primary change in exogenous sodium balance with its attendant osmotic effect or whether it is partly a consequence of an endogenous shift of salt as well as water between the cells and the extracellular compartment. Swingle and his co-workers deduced that adrenal cortical extract increased the isotonic extracellular volume in adrenalectomized, fasted dogs and suggested, therefore, that the adrenal hormone evoked an endogenous shift of salt and water into the extracellular compartment.[1–3] Gaudino and Levitt demonstrated that synthetic desoxycorticosterone produced large but reversible shifts of fluid from within the cells outward whereas adrenalectomy induced the opposite effect.[7] The fact that total body water and serum electrolyte concentrations remained essentially unchanged in their experiments likewise suggested that an endogenous shift of salt and water had occurred. Harrison and Darrow, calculating tissue water compartments upon the assumption that chloride is limited to extracellular distribution, demonstrated that during progressive adrenal insufficiency water shifted from the extracellular to the intracellular compartment but concluded that these water shifts were entirely due to urinary sodium loss and decreased extracellular sodium concentration.[5,6]

The availability of cortisone and ACTH has further stimulated interest in the influence of adrenal activity on electrolyte metabolism. It has been well demonstrated that these agents frequently produce salt retention,[9,10] but it has also been noted that edema and circulatory failure may occur in patients maintained on salt-free diets.[11] As in the case of the other adrenal hormones, it is possible that such effects may result from endogenous salt and water shifts. It seemed desirable, therefore, to study the influence of cortisone and ACTH on fluid and electrolyte distribution in patients maintained on salt-free diets so that primary retention of sodium chloride is minimized if not excluded.

METHODS

Serial measurements of plasma volume, inulin space, serum electrolyte concentrations, and inulin and PAH clearances were performed in six patients before and during the course of cortisone or ACTH therapy. Three of the patients were treated with 100 to 150 mg. of cortisone and three with 100 mg. of ACTH daily for periods of ten to twenty days. Throughout the control period (four to seven days) and the period of hormone treatment the patients were maintained on a rice-fruit diet.‡ The first set of measurements was performed on the last day of the control period and was repeated serially every three to four days throughout treatment. In five of these patients total daily urinary sodium, chloride and potassium outputs were determined. In one patient mercuhydrin was injected daily for three days starting at the sixth day of ACTH treatment but no other phase of the protocol was altered. The patients were weighed daily and adherence to the constant diet was carefully supervised.

Inulin space was measured as previously described.[14–16] Constant priming doses and

‡ Analyses of the rice diet revealed a daily electrolyte intake of 3, 6 and 40 mEq. of sodium, chloride and potassium, respectively, results which compare favorably with previous analyses of the rice diet.[12,13]

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identical infusion rates and concentrations were used in an individual patient throughout the course of a study. The infusion was maintained at a constant rate of 0.8 ± 0.016 cc./min. for five and a half hours. At the end of that time the bladder was washed and the infusion discontinued simultaneously. Thereafter the urine was collected until all the inulin had been excreted (eighteen hours). Three plasma samples were drawn in the ninety-minute interval directly preceding cessation of the infusion. The total amount of inulin excreted after stopping the infusion, divided by the average equilibrium plasma concentration, was taken as the volume of distribution of inulin. Prior to the inulin infusion a plasma blank and a timed urinary specimen were collected for appropriate blank corrections. Virtually all the injected inulin was recovered in the urine (94 to 102 per cent). The quantity of infused sodium chloride that was retained during each space measurement did not exceed 3 per cent of the original store of extracellular sodium and chloride and has been included in the balance data. Inulin and p-aminohippuric acid (PAH) clearances were determined during the final one to two hours of the equilibrating infusion according to the method of Smith and his co-workers.[17]

Analyses for inulin were performed by the Schreiner modification of the resorcinol method[18] and blood glucose and urinary-reducing activity were measured separately in each experiment. No significant hyperglycemia or glycosuria was noted during the course of these observations. Furthermore, the serum and urinary blank corrections preclude any error from this source. PAH determinations were made by the method of Bratton and Marshall.[19] Plasma volume was measured by the T-1824 technic of Gregerson and Stewart with determinations based on a single ten-minute sample.[20] Plasma sodium and potassium concentrations were measured on fasting pre-infusion samples with an internally compensated Perkin-Elmer flame photometer. All such samples from a single patient were analyzed simultaneously at the completion of therapy so that relative changes might be apparent. Urinary sodium and potassium concentrations were likewise measured photometrically. Chloride analyses were performed by the method of Schales and Schales.[21] Total extracellular electrolyte was calculated as the product of the inulin space and plasma concentration. No corrections were made for the water content of serum or for Donnan's equilibrium.

RESULTS

Cortisone and ACTH induced in six patients a progressive increase in the inulin space of distribution. This increase reached its peak after eight to nine days of therapy and averaged 30 per cent (range of 20 to 38 per cent) above control values in the three patients treated with cortisone and 23 per cent (21 to 25 per cent) in the three treated with ACTH. (Table I, Figs. 1 and 2.) The average increase for all six patients equalled 27 per cent. The expansion of inulin space in the cortisone-treated patients was apparent as early as two or three days after the onset of treatment (Cases II and VI) and in all cases was coexistent with a weight loss of 1 to 2 kg. Changes in plasma sodium and chloride were not remarkable although there seemed to be a slight but consistent increase in sodium concentration and either no change or a slight decrease in chloride. The increase in total extracellular sodium and chloride, therefore, approximated the proportionate increase in inulin space. As noted in Table I and Figure 3, the positive sodium chloride balance accounted for only 10 to 20 per cent of the total increase in extracellular electrolyte. If the sodium chloride accumulated from the slight positive balance (including the retained portions of the 50 mEq. of the sodium chloride infused during each inulin space determination) is subtracted from the absolute extracellular electrolyte increase, a substantial moiety remains. This increase in extracellular sodium in the five patients in whom balance data are available averaged 25 per cent, with specific percentages increases for Cases I, II, III, V and VI, respectively, equal to 34, 33, 22, 20 and 20 per cent. Similar increase in extracellular chloride averaged 19 per cent with the individual increments for the same patients, respectively, 28, 21, 22, 11 and 12 per cent. In four patients in whom treatment was continued beyond eight or nine days the inulin space reverted to control values by the twelfth to fifteenth day despite continued therapy (Cases II, III, V and VI). Thereafter, continuation of treatment did not further influence the volume of distribution of inulin. (Table I.) The decrease in extracellular electrolyte which accompanied the decrease in inulin space was not associated with a comparable negative electrolyte balance. The unaccounted for decrease in extracellular

sodium or chloride, therefore, approximated in magnitude the increase detected earlier in treatment. (Figs. 1, 2 and 3.)

Mercuhydrin was injected daily during the sixth to ninth days of ACTH therapy in Case I.

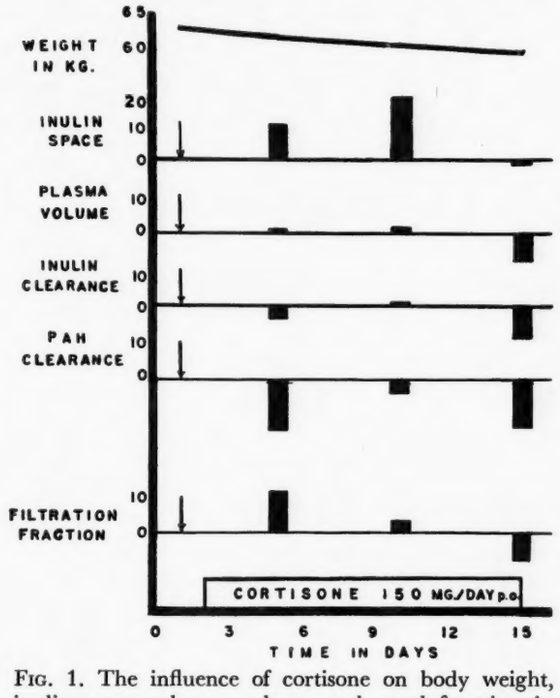

FIG. 1. The influence of cortisone on body weight, inulin space, plasma volume and renal function in Case VI. All indices except weight are expressed as percentile deviation from control.

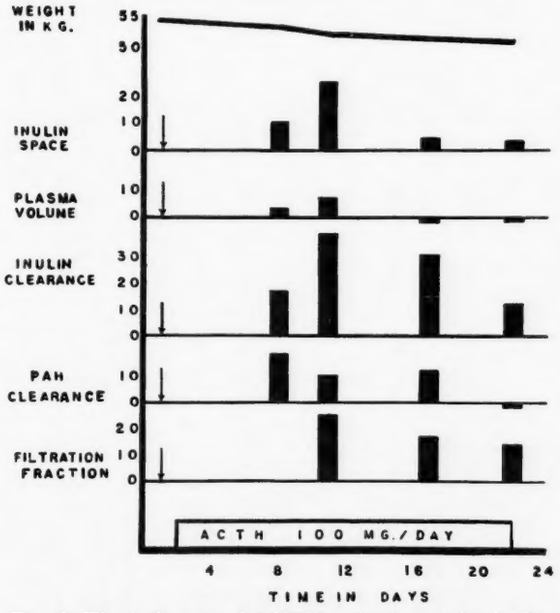

FIG. 2. The influence of ACTH on body weight, inulin space, plasma volume and renal function in Case III. All indices except weight are expressed as percentile deviation from control.

Despite a moderate sodium and chloride diuresis little change was noted in the inulin space.

In three of the five patients (Cases I, II and III) in whom balance studies were performed a negative potassium balance of about 20 mEq./

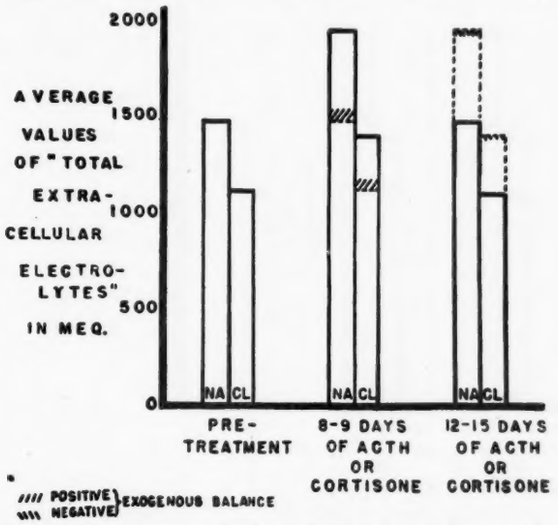

FIG. 3. The average absolute changes in total extracellular electrolyte during cortisone and ACTH therapy compared to simultaneous changes in exogenous balance.

day was noted during the first two or three days of hormone treatment. Thereafter no demonstrable negative or positive potassium balance was present except in the patient who received mercurial diuretics. Here a negative balance of 125 mEq. was produced during the three-day period of electrolyte diuresis.

The changes in plasma volume were conspicuously small and probably within the range of experimental error. There was an increment in plasma volume which averaged 6 per cent, with a range from 2 to 10 per cent. (Table I.)

Renal function studies revealed a progressive increase of filtration rate in six of seven patients. (Table I.)* Simultaneously, PAH clearances showed variable changes with slight increase in some and decrease in others. Cortisone and ACTH therapy, therefore, produced an increase in filtration fraction in each patient. The average increase in glomerular filtration rate was 31 per cent, in filtration fraction 23 per cent. Peak increases in renal function generally coincided with maximal expansion of the inulin space. Renal function reverted to control or subcontrol levels as adrenal therapy was continued beyond eight or nine days.

* The renal function data obtained without coincident space measurements are not included in the tables.

TABLE I

EFFECTS OF ACTH AND CORTISONE ON THE DISTRIBUTION OF WATER AND ELECTROLYTES IN THE BODY FLUIDS

Observation	Weight (kg.)	Inulin Space (L.)	Inulin Space % of Body Wt.	Serum Electrolytes (mEq./L.) Na	Serum Electrolytes (mEq./L.) K	Serum Electrolytes (mEq./L.) Cl	Total Extracellular Na (mEq.) (a)	Exogenous Na Balance between Observations (mEq.) (b)	Total Extracellular Cl (mEq.) (c)	Exogenous Cl Balance between Observations (mEq.) (d)	Unaccounted for Change in Extracellular Electrolytes (mEq.) Na (Δa–b)	Unaccounted for Change in Extracellular Electrolytes (mEq.) Cl (Δc–d)	Plasma Volume (cc.)	Renal Function C_{In}	Renal Function C_{PAH}	Renal Function F. F. (%)
Case I; female; age 52; non-toxic adenoma of the thyroid																
Control	57.7	10.0	17.3	147	3.9	107	1,470		1,070				3,170	97	492	19.7
6 days of ACTH, 100 mg./day	56.8	12.3	21.6	149	4.2	106	1,830	+38	1,300	+22	+322	+208	3,290	110	502	21.9
9 days of ACTH, 100 mg./day, 3 days of daily mercuhydrin, 2 cc. i.m.	55.0	12.1	22.0	149	4.1	94	1,800	-213	1,140	-252	+183	+ 92	3,350	149	620	24.0
											Total +505	+300				
Case II; female; age 38; bronchial asthma																
Control	58.0	13.3	22.9	146	4.2	109	1,940		1,450				2,270	138	440	31.4
2 days of cortisone, 150 mg./day	57.4	15.7	27.4	146	3.8	107	2,290	+38	1,680	+41	+312	+189		141		
6 days of cortisone, 150 mg./day	57.2	16.4	28.7	149	3.6	103	2,440	+48	1,690	+45	+102	- 35	2,560	142	393	36.2
9 days of cortisone, 150 mg./day	56.5	17.9	31.6	151	3.2	104	2,700	+39	1,860	+18	+221	+152	2,440	194	450	43.2
											Total +635	+306				
15 days of cortisone, 150 mg./day	56.0	12.0	21.4	148	3.7	107	1,770	+20	1,280	-12	-950	-568	2,520	90	370	24.3
20 days of cortisone, 150 mg./day	55.7	12.3	22.0	147	3.7	105	1,810	+35	1,290	+14	+ 5	- 4	2,440	104	355	29.3

Case III; female; age 26; no disease																
Control	54.3	11.0	20.2	151	4.1	110	1,660		1,210				2,570	103	500	20.6
6 days of ACTH, 100 mg./day	53.2	12.1	22.8	154	3.9	110	1,860	+36	1,330	+16		+164	+104	2,650	122	592	20.6
9 days of ACTH, 100 mg./day	52.5	13.7	26.1	152	3.8	110	2,080	+19	1,510	+18	Total	+201 +365	+162 +266	2,760	142	550	25.8
15 days of ACTH, 100 mg./day	51.8	11.4	22.0	150	3.7	108	1,710	-54	1,230	- 2		-316	-278	2,530	135	560	24.1
20 days of ACTH, 100 mg./day	51.2	11.4	22.2	146	3.2	105	1,670	-10	1,200	- 6		- 30	- 24	2,540	116	490	23.7
Case IV;* female; age 21; bronchial asthma																
Control	56.0	8,600 (cc.)	15.4													
9 days of cortisone, 100 mg./day orally	54.0	11,900 (cc.)	22.0													
Case V; female; age 45; mild hyperthyroidism																
Control	61.0			145	4.1	107								2,140	112	590	19.0
3 days of ACTH, 100 mg./day	60.5	9.5	15.7	144		105	1,370		998						128	480	26.7
6 days of ACTH, 100 mg./day	59.4	10.5	17.7	144	3.9	105	1,510	+24	1,100	+36		+116	+66	2,360	128	515	24.9
8 days of ACTH, 100 mg./day	58.8	11.5	19.6	147	4.0	102	1,690	+20	1,170	+28	Total	+160 +276	+42 +108		147	500	29.4
12 days of ACTH, 100 mg./day	57.8	8.7	15.0	141	4.1	109	1,230	-52	948	-20		-408	-202	2,100	110	502	21.9
Case VI; female; age 21; no disease																
Control	63.0	9.5	15.1	146	4.4	110	1,390		1,050					2,350	120	665	18.1
3 days of cortisone, 150 mg./day orally	62.0	10.6	17.1	152	4.0	108	1,610	+10	1,150	+14		+210	+86	2,330	115	552	20.8
8 days of cortisone, 150 mg./day	60.7	11.4	18.8	148	4.0	106	1,690	+26	1,210	+30	Total	+ 54 +264	+ 30 +116	2,400	121	639	19.0
13 days of cortisone, 150 mg./day	59.6	9.3	15.6	145	4.1	107	1,350	-40	990	-20		-300	-200	2,150	93	558	16.7

C_{In} = Plasma clearance of inulin in cc./min. C_{PAH} = Plasma clearance of para-aminohippuric acid in cc./min. F. F. = Filtration fraction.

*No balance studies were performed in this patient.

The changes produced by cortisone and ACTH were qualitatively similar. Because of variation in dosage, the undetermined factor of dosage equivalence and the inherent limitations of the methods it is impossible to conclude that these agents produce quantitatively different responses. Consequently, the data from the two groups of patients have been treated as essentially one group of experimental observations.

COMMENTS

Available evidence suggests that the space of distribution of inulin affords the most reliable estimate yet made of the true extracellular volume.[14–16,22,47] This conclusion is deduced from two separate lines of investigation; one purporting to demonstrate that inulin is completely excluded from the cells, and the other that it is freely diffusible throughout the extracellular compartment. That inulin does not enter cells seems probable *a priori* in view of its average molecular weight (5,000),[23] its elongate structural configuration[24] and its lipoid insolubility. The inulin molecule has been shown to be excluded from erythrocytes,[25] bile,[26] gastric juice[27] and renal tubular cells.[25] No enzymes are known to be present in man which are capable of hydrolyzing it,[25] and its rapid and quantitative recovery in the urine[14,16,28] argues against any significant storage or metabolism in the living organism. Its space of distribution is smaller than simultaneous volumes of other substances (thiocyanate, sodium, chloride, mannitol) used for the measurement of extracellular fluid, most of which are now known to enter cells or undergo partial metabolism.[22,29–31] The volume of distribution of inulin, as a measure of extracellular fluid, is therefore more readily compatible with recent estimates of total body water.[32,33]

The alternate possibility of incomplete diffusion into the extracellular compartment is made improbable by two sets of experimental observations: (1) Once the minimum infusion time necessary to establish equilibrium distribution of inulin has been established (two hours in the dog, five hours in man), further prolongation of the infusion does not increase its space of distribution.[15,16] (2) The volumes of distribution of sucrose and inulin in the nephrectomized rabbit and rat,[26,34] and mannitol (with corrections for metabolism) and inulin in the human are identical.[22,31,35] The equality of the spaces of distribution of molecules of such great variation in size offers strong evidence against the possibility of extracellular compartmentalization.

In the experiments herein described cortisone and ACTH produced significant increases in the inulin space. That these changes were not attributable to the metabolism of inulin is confirmed by the virtually complete recovery of the infused inulin which was achieved in each experiment. Inasmuch as these alterations were not associated with comparable weight changes or exogenous sodium or chloride balance only two alternative explanations are possible: (1) Cortisone and ACTH induce an internal redistribution of salt and water. (2) These agents produce an alteration in cellular permeability so that the inulin molecule is temporarily accessible to a small proportion of body cells (10 to 15 per cent). The second alternative is rendered unlikely by the evidence cited to support the hypothesis that inulin is excluded from cells. Furthermore, it seems improbable that a carbohydrate molecule of such size may enter cells without undergoing breakdown or metabolism. This alternate explanation, however, cannot be completely excluded at this time.

If it is accepted that the inulin volume of distribution provides a reliable estimate of extracellular volume, it follows as an immediate corollary that cortisone and ACTH induce an internal redistribution of salt and water. The following considerations are based on this premise:

The endogenous sodium and chloride emptied into the extracellular compartment during the first eight to nine days of cortisone or ACTH therapy increased the total amount of extracellular electrolyte by 25 and 19 per cent, respectively. These average figures define the proportion of sodium and chloride originally contained within the extracellular compartment as approximately 80 and 84 per cent, respectively, of the amounts contained therein at the point of peak response. Previous observations regarding the proportion of extracellular sodium to total body sodium (simultaneous inulin/sodium space ratios) have yielded average ratios of 0.62 in man and dog.[15,16,36] Similar inulin/chloride space ratios in the dog (not performed simultaneously) have averaged 0.76,[15,37] or if, as previously suggested, bromide be used as a measure of total body chloride, 0.67.[14,38] No simultaneous over-all inulin/chloride space ratios are available in man. Recently, however,

it has been shown that the inulin/chloride space ratio in human muscle tissue averages 0.82[39] despite the circumstance that muscle cells are relatively chloride-free.[29] Simultaneous inulin/bromide space ratios in man approximate 0.60 to 0.70.[16,33] Consequently, the quantity of sodium and chloride contained outside of the inulin space appears entirely adequate to account for the average changes described. The magnitude of the chloride shift was proportionately smaller than the simultaneous sodium movement, possibly as a result of the disparity between the proportion of non-extracellular chloride and sodium.

The artificial diuresis produced by mercuhydrin in Case 1 did not obscure the hormone-induced changes. The mercurials were administered before the expected peak increase in inulin space and, although a moderate sodium and chloride diuresis was induced, the fall in total extracellular electrolyte was disproportionately small. The artificial diuresis, therefore, did not prevent the movement of sodium and chloride into the extracellular compartment.

In three patients a mild and transient negative potassium balance occurred during the early phase of the sodium and chloride shift into the extracellular compartment. Otherwise no clear-cut relation was observed between the redistribution of sodium and chloride and exogenous potassium balance.

These experiments do not reveal the precise source of the endogenous water, sodium and chloride which are diverted into the extracellular compartment. The known calcium and phosphorus mobilization which is induced by the adrenal steroids[10,40] suggests that some of the sodium may derive from bone, which is known to contain appreciable stores of sodium. The quantity of salt-containing fluid present in the small intestine is another potential source and, of course, some tissue cells may contribute a significant proportion. The mechanism of reversal of this redistribution with continued cortisone or ACTH therapy is also unknown.

The changes in plasma volume are extremely small and possibly within the range of experimental error. What may be of significance is that each patient showed an increase, albeit small, coincident with the expansion of the extracellular volume. Certainly, as has been previously noted, plasma volume does not offer a sensitive index of changes in the extracellular volume.[7,41]

In six of the seven patients studied there was a significant increase in filtration rate and, in all seven, an increase in filtration fraction similar to observations previously recorded.[42–44] It has been shown that the rice diet itself may produce alterations in renal function but in opposite direction from those observed here.[45,46] This circumstance may account for the subcontrol values noted after twelve to fifteen days of cortisone or ACTH therapy. Although the peak changes in renal function and inulin space generally coincided, it does not follow that they are causally related. In Case 1 further expansion of the extracellular volume was inhibited by mercurial diuretics but a progressive change in renal function occurred nevertheless. This observation suggests that the adrenal hormones may influence body water and electrolyte distribution and renal function simultaneously but independently.

SUMMARY

1. Cortisone and ACTH induce a transient shift of water, sodium and chloride into the measurable extracellular volume (inulin space).

2. This redistribution reaches its peak after eight to nine days of cortisone or ACTH therapy and then regresses despite continuation of therapy.

3. Cortisone and ACTH produce a progressive increase in glomerular filtration rate and filtration fraction. The maximal changes in body fluid distribution and renal function coincide.

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Experience with Methimazole (Tapazole) in the Treatment of Hyperthyroidism*

A Report of Thirty-five Cases

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THE introduction of antithyroid drugs into the treatment of hyperthyroidism has greatly improved the prognosis and course of patients with this disease. The earliest substances used as antithyroid agents proved to be moderately toxic, but recently, with the introduction of 6-n-propyl-2-thiouracil and 4-methyl-2-thiouracil, the problem of toxicity has been greatly reduced. Both of the newer agents, however, have proved to be toxic in a small number of cases[1–5] and the search for less dangerous materials continues.

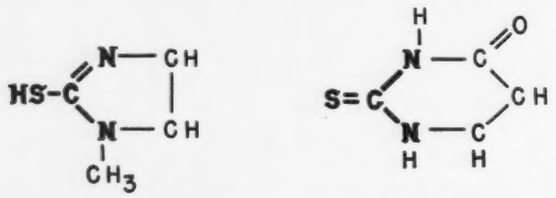

FIG. 1. Structural formulas of thiouracil and methimazole. Dark portions represent the thiourea nucleus, which is probably responsible for antithyroid activity.

Stanley and Astwood[6] in 1947 screened thirty-two compounds for antithyroid activity and showed that the most potent material when tested in man was 2-mercaptoimidazole. Further studies of mercaptoimidazole derivatives showed that 1-methyl-2-mercaptoimidazole (methimazole, "tapazole") is even more active, being approximately 100 times as effective as thiouracil.[7]

The mercaptoimidazole group of goitrogens differs from the thiouracil group structurally in that the former possesses a five-member ring whereas the thiouracil ring has six atoms. The basic thiourea grouping, which is present in both molecules, is probably responsible for their activity. (Fig. 1.) The mode of action of the two types of goitrogens is therefore similar.

The high potency of methimazole suggested that it might be less toxic than any of the other antithyroid medications since the required dose would be very much less than for the other substances. Preliminary reports on the effects of the medication in hyperthyroidism looked promising.[8,9] A series of patients was therefore treated with methimazole and their response, course and toxic reactions evaluated.

MATERIAL AND METHODS

Thirty-five patients with proved hyperthyroidism were studied. (Table I.) All of the patients at Grady Memorial Hospital in whom the diagnosis of hyperthyroidism was first made between July, 1950, and April, 1951, were included in the study. The diagnosis of hyperthyroidism was based upon the clinical picture, the serum protein-bound iodine concentration (PBI) and, in many cases, on the basal metabolic rate and I^{131} uptake. The unreliability of the basal metabolic rate and the ready availability of the protein-bound iodine determination[10] led us to rely more on the latter; however, it was never accepted blindly without adequate clinical evidence of toxicity in the form of tachycardia at rest, heat intolerance, weight loss or changes of the hair and skin texture. In most cases all of these changes were observed and in almost all instances a definite goiter was also palpable.

In addition to this series a few patients were included from other hospitals. These patients were all seen personally by one of the authors, and the criteria for diagnosis were similar to those outlined for the Grady group.

None of the patients studied in this series had been receiving any other antithyroid medication before the administration of methimazole was begun. One patient had received propylthiou-

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racil one year previously but had eloped from the clinic and had received no medication for a year when methimazole was started.

RESULTS

Effect on Hyperthyroidism. Of the thirty-five patients treated with methimazole all but one showed dramatic improvement. (Table I.) The single exception was a fifty-eight year old man with severe congestive heart failure, who died of his cardiac disease after less than one week of therapy. During this time his serum protein-bound iodine had dropped from 16.6 to 11.7 micrograms/100 ml., indicating that he had begun to respond to the medication.

The remaining thirty-four patients were evaluated critically at one-week intervals for three or four weeks and thereafter at two-week intervals. An attempt was made to estimate the time required for control of hyperthyroidism by determining the approximate date at which the patient first became "euthyroid." Obviously such an estimate is subject to considerable error; but since the criteria for euthyroidism were standardized and the evaluations were performed by the same observers, it seems likely that they have a rough validity. It took from two to twenty-two weeks to control the toxic symptoms completely. During this time all of the patients gained weight (from 4 to 36 pounds, average 15.5 pounds) except for eight patients who had been in congestive failure when treatment was started. In this group evaluation of weight changes was complicated by the presence of edema, which invariably disappeared during therapy. The weight change in the patients with heart disease varied from a loss of 15 pounds to a gain of 11 pounds. The pulse rate became less rapid in all patients. In those with normal cardiac function the heart rate was reduced from 10 to 55 beats per minute (average 30); when congestive failure was present, the decrease was similar but its significance is difficult to evaluate because many of these patients also had auricular fibrillation, and an accurate estimation of the mean pulse rate was difficult.

Methimazole caused a rapid decrease in the serum protein-bound iodine. There was a poor correlation between the fall of PBI and clinical improvement of the patient. The reduction of PBI often occurred before the patient improved clinically, an observation which has been noted previously.[10] The chief value of the PBI under these circumstances was to indicate that the circulating thyroid hormone concentration was kept within normal limits until the peripheral metabolism could fall to normal. By following the PBI it was possible to avoid the development

TABLE I

CLINICAL DATA PERTAINING TO THIRTY-FIVE PATIENTS TREATED WITH METHIMAZOLE

1. Age	3 to 69 (avg. 39.6)		
2. Sex	12 males (34%)		
3. Race	21 colored (60%)		
4. Initial PBI (micrograms.100 ml.)	9.3 to 28.7 (avg. 15.5)		
5. Initial basal metabolic rate	+28 to +96 (avg. +58); test available in only 25 patients		
6. Results of therapy	Euthyroid	33	
	Improved but not yet euthyroid	1	
	Dead	1	
7. Maximum dose of methimazole		Smooth goiters	Nodular goiters
	10 mg./day	1	
	20 mg./day	17	7
	30 mg./day	4	
	40 mg./day	3	2
	60 mg./day	1	
8. Duration of therapy to euthyroidism	Smooth goiters (26)	8.8 ± 1.1 wk.*	
	Nodular goiters (9)	8.2 ± 2.2 wk.	
9. Change during therapy (from initial observation to euthyroid state)	Weight +4 to +36 (avg. +15.5)†		
	PBI −0.4 to −21.2 micrograms % (avg. 7.8 micrograms %)		
	Pulse −10 to −55 (avg. 30)†		
10. Final disposition of euthyroid group	Subtotal thyroidectomy	22	
	Radioactive iodine	9	
	Prolonged medical treatment	3	

* Mean ± standard error of the mean.

† Eight patients with congestive failure were omitted from these figures.

of myxedema, and clinical relapses could be predicted and prevented by observing a sudden rise of PBI before any change in the clinical status had occurred. During the course of therapy the PBI fell 0.4 to 21.2 micrograms/100 ml. (average fall was 7.8 micrograms/100 ml.).

Dose. The dosage of methimazole varied from 20 to 60 mg. per day, in divided doses of 5 mg. Table 1 shows how the doses were distributed. In general, a dose of 20 mg. per day was adequate; but if the PBI failed to show improvement within a week or two, it was usually increased to 30 or 40 mg. per day. In only one case were 60 mg. per day given—to a woman whose response to 40 mg. per day for eleven weeks had been inadequate. Since this patient was rather uncooperative, it is not certain that she had actually been taking the prescribed dose. On admission to the hospital the dose was raised to 60 mg. and at this level she showed rapid improvement and was ready for subtotal thyroidectomy within a week.

The patients with nodular goiter did not require any larger dose of methimazole or longer treatment than did the patients whose goiters were not nodular. (Table 1.) This is contrary to the experience with propylthiouracil, which has often proved to be relatively ineffective in patients with large or nodular goiters.

Toxicity. No toxic reactions were observed among the patients receiving methimazole. A specific search for leukopenia, agranulocytosis, fever and rash was made each time the patients were seen in the clinic. None of these complications were observed In no case was it necessary to stop or reduce the dose because of toxic complications.

In addition to the main series of patients, methimazole was also administered to two patients in whom toxic manifestations had previously developed while propylthiouracil was being received. In these cases methimazole was well tolerated.

CASE REPORTS

CASE 1.* A sixty year old woman was admitted with classical symptoms and signs of thyrotoxicosis complicated by congestive heart failure and rapid auricular fibrillation. She had a large, smooth goiter. Her basal metabolic rate was +85 and her serum PBI was 14.9 micrograms/100 ml.

Treatment was started with 300 mg. propylthiouracil daily in divided doses. After one week of therapy a fever of 103°F. developed which persisted for a week and disappeared within twenty-four hours after stopping the propylthiouracil. The propylthiouracil was resumed two days later and the dose increased to 400 mg. per day without return of the fever. After three weeks of therapy the PBI was 15.9 micrograms/100 ml. and the basal metabolic rate +75. The white count remained normal throughout. In the fourth week of treatment the patient was found to have a white count of 4,000 and propylthiouracil was promptly discontinued. The next day a severe sore throat developed, with ulceration of tonsils and palate. The temperature rose to 100.4°F. and the white count was found to be 3,650, with 2 per cent mature segmenters, 4 per cent myelocytes and 4 per cent premyelocytes. The white count returned to normal after three weeks of supportive and antibiotic therapy but thyrotoxicosis became worse. At this time treatment with 5 mg. methimazole four times daily was started. Within five days the PBI had dropped to 10.7 micrograms/100 ml. One month later the hyperthyroidism was greatly improved, no granulocytopenia had developed and the patient was being prepared for thyroidectomy.

Comment. In this patient large doses of propylthiouracil failed to control the hyperthyroidism but did produce serious agranulocytosis. Methimazole produced prompt improvement of the thyrotoxicosis and failed to cause toxic symptoms.

CASE II.* This fifty-six year old farmer was admitted to the hospital because of a hemolytic streptococcus bacteremia which responded well to antibiotic therapy. On recovery it was apparent that he also had typical signs of hyperthyroidism. The serum PBI was 16.4 micrograms /100 ml. and the BMR +68. Treatment was begun with 375 mg. propylthiouracil per day, and the dose was increased to 500 mg. per day nineteen days later. On the twenty-fourth day of therapy he began to spike daily fevers of 103° to 104°F. Blood cultures were sterile and penicillin failed to control the fever. The propylthiouracil was therefore stopped and the fever subsided within a few days. A second trial of propylthiouracil therapy was begun after the temperature had been normal for three days. After ten days of treatment the spiking fever

* We are grateful to the staff of Piedmont Hospital, Atlanta, Ga., for permission to report this case.

* The staff of Lawson Veterans Hospital kindly supplied the clinical data.

returned and continued for a week until propylthiouracil was discontinued. Five days later 20 mg. of methimazole per day were started and continued without difficulty for a month, at which time his PBI was 6.4 and he appeared euthyroid. He was then given a therapeutic dose of 10 mc./I^{131}.

Comment. Drug fever developed twice when the patient was given propylthiouracil. He was able to take methimazole without difficulty and had an uneventful recovery.

Potency Compared with Propylthiouracil. In view of the excellent effectiveness and apparent lack of toxicity of methimazole it seemed desirable to compare its potency with that of propylthiouracil. With this in mind we have studied a group of fifty patients previously treated with propylthiouracil during the two years prior to the present series. These patients were selected at random from the files of the Grady Memorial Hospital endocrine clinic and represent a fair cross section of the clinic population suffering from hyperthyroidism observed from January, 1948, to June, 1950. (Table II.) The propylthiouracil-treated group was examined to eliminate patients who received inadequate dosage of the drug (less than 300 mg. per day was considered inadequate)[11] or who had suffered complications which might have interfered with a smooth convalescence under the influence of the goitrogen. Four cases were dropped; one because of inadequate dosage, one because of pregnancy and two because of agranulocytosis.

Forty-four of the remaining forty-six patients became euthyroid after a course of treatment lasting six to 104 weeks (average thirty; standard error 3.6). When this is compared with the duration of treatment for the methimazole-treated group (average 8.5 $\pm$0.9 weeks) the difference proves to be highly significant ($p < .01$).[12] The dose of propylthiouracil ranged from 300 to 700 mg. per day—more than ten times the amount of methimazole required. There were two instances of leukopenia in the fifty cases, an incidence of 4 per cent of potentially serious toxicity, as compared with the complete absence of toxicity in the methimazole group.

TABLE II

CLINICAL DATA PERTAINING TO FIFTY PATIENTS TREATED WITH PROPYLTHIOURACIL IN 1948–1950

1. Age	15 to 77 (avg. 40.3)	
2. Sex	13 males (26%)	
3. Race	34 colored (68%)	
4. Maximum dosage	Less than 300 mg./day	1
	300 to 390 mg./day	16
	400 to 490 mg./day	20
	500 to 590 mg./day	5
	600 mg. or more/day	7
5. Duration of therapy until euthyroid state	6 to 104 wk. (avg. 30 $\pm$ 3.6* wk.)	
6. Results of therapy	Euthyroid	46
	Stopped therapy because of agranulocytosis	2
	Therapy incomplete	2

* Standard error of the mean.

Ultimate Disposition of Treated Patients. Hyperthyroid patients who have been brought to the euthyroid state can be carried on maintenance doses of antithyroid medication for prolonged periods in the hope that a permanent remission will occur; or they can be treated in a definitive manner by either subtotal thyroidectomy or irradiation with I^{131}. It is the practice of this clinic to give almost all hyperthyroid patients some form of definitive therapy because the nature of the clinic population makes it inadvisable to embark on a course of therapy which may continue over a period of many months. Of the patients in this series, therefore, twenty-two have been subjected to subtotal thyroidectomy and nine have received radioactive iodine. Final disposition has not been determined for the remaining four patients.

*Effect on Morphology of Thyroids Removed at Operation.** Eighteen thyroid glands were available for pathologic study. They varied in weight from 18 to 160 gm., the average weight being 53 gm. Seven glands displayed a distinctly nodular architecture on gross examination.

A minimum of five tissue blocks were prepared from each gland. Tissues were fixed in Zenker's fluid with 5 per cent glacial acetic acid and were stained with phloxine and hematoxylin.

The glands of fourteen patients showed histologic changes of active hyperplasia. In most

* This section was prepared by Dr. Abner Golden, Pathologist of Emory University Hospital, who reviewed all of the histologic slides available on these patients.

areas the follicular epithelium had a tall columnar appearance; it occasionally projected into the follicular spaces as small papillary infoldings. The nuclei were prominent and slightly pleomorphic, and mitotic figures were not infrequently encountered. Some nuclear fragmentation, cell degeneration and desquamation were apparent but these changes were unaccompanied by an inflammatory reaction. The follicles were generally decreased in size and contained pale staining, vacuolated or "scalloped" colloid. A distinct increase in stromal vascularity frequently occurred.

The glands of four patients revealed marked involution, indicated by large colloid-filled follicles lined by flat or low cuboidal epithelial cells. Three of these patients had received preoperative iodine therapy. None of the glands showed evidence of neoplastic change.

The histologic findings of active glandular hyperplasia are entirely comparable to those described following the administration of thiouracil to patients in the euthyroid or hyperthyroid states.[13,14]

Effect of I^{131} Uptake. The patients who received radioactive iodine received no methimazole for three days before the administration of I^{131}, in accordance with the recommendations of Williams et al.[15] Estimates of the percentage uptake of radioiodine were made in each case by direct counting over the neck, using a Geiger-Müller tube at 1 meter. The radioactivity over the neck was compared with the radioactivity of the therapeutic dose, counted before administration and extrapolated to twenty-four hours later on the I^{131} decay curve.* Measurements were made twenty-four hours after the administration of the therapeutic dose, which ranged from 4 to 8 mc. The uptake by methimazole-treated patients was 56 ± 6.9 per cent (range 40 to 85 per cent), which is approximately the same as that seen in hyperthyroid patients before treatment (>31; average 54) and is definitely higher than the normal value (range 7 to 35; average 21). It is thus apparent that preparation of the patient with methimazole prior to irradiation of the thyroid gland with radioactive iodine does not interfere with the uptake of the isotope, nor with successful irradiation of the gland.

* The data pertaining to I^{131} uptakes were generously supplied by Dr. Charles M. Huguley and Mr. William Miller of the Winship Clinic and Surgical Research Laboratory, Emory University, who also were responsible for the treatment of these patients with I^{131}.

COMMENTS

When a new drug is introduced for the treatment of hyperthyroidism, it must satisfy several criteria to justify acceptance. It should be less toxic than the medications already in use; it must be at least as effective; and it should not interfere with further therapeutic maneuvers such as subtotal thyroidectomy or irradiation with I^{131}.

In the group of patients treated with methimazole no instance of toxicity has been observed; in two cases methimazole proved to be non-toxic in patients who had had reactions to propylthiouracil. The number of patients studied, however, is too small to justify a categorical statement that methimazole is non-toxic; indeed, it seems almost certain that when a sufficiently large number of patients have been treated with the drug, toxic manifestations will appear. On the basis of our experience, however, it seems unlikely that the incidence of toxic manifestations will be as great as that found with propylthiouracil. One factor of importance in the low incidence of toxicity is probably the relatively small quantity of methimazole required to produce a therapeutic response. Not only is the daily dose about one tenth as large as the minimum effective daily dose of other antithyroid compounds but also the response is so rapid that the period of treatment required to attain the euthyroid state can be shortened substantially. As a result, the patient is exposed to a smaller amount of medication for a shorter period of time than when propylthiouracil is used.

The administration of methimazole is followed by a rapid improvement in the signs and symptoms of hyperthyroidism. We have attempted to compare the rate of response to methimazole with the rate of response to propylthiouracil. Since the methimazole-treated group was not studied simultaneously with the propylthiouracil-treated patients, the two groups cannot be considered completely comparable. Supervision of the methimazole group may have been somewhat closer than of the propylthiouracil patients, and other unrecognizable differences between the groups may have biased the results somewhat. In spite of these reservations as to the validity of the comparison it still seems probable that the response to methimazole was more rapid than to propylthiouracil. Since the drugs act in a similar fashion, it is difficult to explain this difference. The factor limiting the rate of response of a thyrotoxic patient to an

agent blocking the formation of thyroxin should be the rate of destruction of thyroxin by the tissues and the rate of dissipation of the effects of the hormone. There is no evidence to suggest that either methimazole or propylthiouracil affects the peripheral metabolism of thyroxin. The simplest explanation of the discrepancy, therefore, is that methimazole blocked the formation of thyroxin more nearly completely than did propylthiouracil. The difference may merely be one of dosage; but if this is the case, the effectiveness of methimazole must be even more than ten times as great as propylthiouracil.

It is a matter of considerable importance to be certain that an antithyroid drug does not complicate the task of the surgeon. For the most part, the patients operated upon in the present study received iodine for two or three weeks prior to operation. With this premedication the surgeons found the thyroids to be relatively easy to handle. Excessive vascularity and friability of the gland did not occur. In two cases operation was carried out without prior iodine prepation. In these cases the glands were somewhat friable and vascular, which discouraged the surgical staff from further attempts to operate without iodine medication.

The use of goitrogens in preparation for the administration of I^{131} may not be necessary in every case. However, it is known that irradiation causes a temporary increase in the circulating thyroxin[16] and that exacerbations of hyperthyroidism have occasionally occurred following irradiation. This may make it desirable to bring the patient to an euthyroid state before irradiating the gland, particularly when the patients in question have heart disease or are otherwise debilitated, as was the case in most of the patients who received I^{131} in this series. It is therefore important to find that preparation of patients for radioiodine therapy with methimazole does not interfere with the effectiveness of this type of therapy.

SUMMARY

1-methyl-2-mercaptoimidazole (methimazole, "tapazole")* has been used in the treatment of thirty-five patients with hyperthyroidism. A good therapeutic response occurred in all cases. No toxic effects developed. Most patients responded to a dose of 5 mg. four times daily; occasionally as much as 40 mg. per day were given. The rate of response was significantly faster than for a group of fifty patients treated with propylthiouracil. Methimazole in combination with iodine provided satisfactory preparation for subtotal thyroidectomy. The drug did not interfere with the uptake of radioactive iodine in therapeutic amounts.

Methimazole ("tapazole") appears to be the antithyroid drug of choice at the present time.

* Kindly supplied by Dr. D. C. Hines, Eli Lilly & Co., Indianapolis 6, Ind.

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Seminars on Arteriosclerosis

Arteriosclerosis—Some Clinical Implications*

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THE great upsurge of interest in and hope for the control of atherosclerosis should not blind the clinician to the fact that this is only one facet of the problem of arteriosclerosis, and that arteriosclerosis is only one factor in the loss of function encountered in an aging population. Since arteriosclerosis of various types has predilection for various sites, the emphasis in this discussion will be on local manifestations and on the interplay between arteriosclerosis and involutional changes of other sorts in leading to symptoms, signs and dysfunction.

BRAIN

When we observe cerebrovascular accidents occurring in subacute endocarditis and in auricular fibrillation in people under thirty years of age, we are impressed by the lack of change in personality, in spite of a chronic illness, progressive crippling and repeated insults to the brain. On the other hand, in people over fifty and especially in those over seventy, we are struck by the loss of interest, energy and judgment which so often follows small cerebrovascular accidents. Alvarez,[1] in his contributions to the problem of "little strokes" with great deterioration in personality and with outstanding digestive or "neurotic" complaints, has cited many of these instances in which repeated strokes, with negligible neurologic disturbance, caused bizarre and misdiagnosed illnesses. At autopsy the elderly subjects have disseminated cortical atrophy and dilated cerebral ventricles as a result of involutional changes, as well as focal softening or hemorrhage, while the young ones have only focal lesions. We conclude that when the brain is young and its neurone content high, cerebral accidents produce much less change in personality than when the brain is already atrophic from involutional loss of neurones.

Avitaminosis, combined system disease and hypothyroidism are other factors which accentuate the functional effects of cerebral anoxic injury. In combined system disease and in cortical atrophy the Schmidt-Kety method reveals practically normal blood flow, with low O_2 and glucose uptake.[2] Those factors which are reversible with therapy, or at least held in check while the patient adjusts himself to his disability, must always be in the clinician's mind, along with the environmental stresses peculiar to aging, namely, retirement, loss of relatives and friends, declining buying power of fixed incomes, conflicts with children and aggressive young associates. Evaluation of the role of cerebral arteriosclerosis and of "little strokes" in the development of senile dementia and psychoneuroses is difficult even with a good history and a complete autopsy. During life we must not ascribe to cerebral vascular disease all the manifestations of cerebral aging, which may in part be reversible with B_{12} or other water-soluble vitamins, or greatly improved by correcting the social environment and the attitude of relatives and associates.

The cerebral arteries are subject to several types of sclerosis. The simplest is the intimal proliferation which occurs with syphilitic mesarteritis or the periarteritis of diffuse vascular disease or of tuberculous meningitis. Any of these may predispose vessels in the meninges to thrombosis or to occlusion hastened by atheroma developing secondarily. Similar internal thickening and secondary atherosclerosis occurs in aneurysmal weakening of basal arteries on a congenital basis. In the small arteries in the brain substance calcific or cystic medial disease and endarterial proliferation follow cortical atrophy and predispose the vessels to minute atheromas and to rupture. Thus the cerebral involution which accentuates functional loss from small strokes also plays a part in the pathogenesis of the vascular disease which causes such

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accidents. Familial tendency to cerebral arteriosclerosis, rather than coronary disease, may be due in part to the pattern of cortical aging and in part to body build. Wilens has correlated low intracranial pressure, due to the upright posture and a relatively long spinal canal, with the relatively high ratio of cerebral to coronary accidents.[3]

RETINA

While the branches of the ophthalmic artery are not free from disease due to syphilis, tubercles or other inflammatory lesions, they suffer chiefly from "degenerative" lesions associated with hypertension, nephritis and diabetes. Cystic degeneration of the retina may predispose to vascular disease in the same way as cortical atrophy, but for the most part aging normotensives show only tortuosity of the arteries, without focal vascular lesions. It is a curious fact that in uremia and hypertension associated with chronic pyelonephritis or congenital cystic disease of the kidneys retinal sclerosis is somewhat less marked than in uremia due to glomerulonephritis. In some middle-aged uremics with these diseases the retina may be practically normal as it is in obstructive uropathies. When hypertension or diabetes precedes proteinuria by several years, retinal vascular disease is nearly always severe when urea retention is marked. The retina, like the kidney, has a high rate of blood flow per gram of functioning tissue, and in diabetes both organs show lesions far out in the arteriolar system, or even in the capillaries and juxtacapillary venules. In toxemia of pregnancy and malignant sclerosis the arterial component in the retina is complicated by papilledema and venous engorgement due to high intracranial pressure.

KIDNEYS

Three types of arteriosclerosis are manifested in the renal arterial bed, namely, reduplication of the medial elastica, atherosclerosis and regenerative intimal thickening due to atrophy or to adjacent foci of inflammation. In chronic pyelonephritis, glomerulonephritis, periarteritis and disseminated lupus all three processes are at work simultaneously in most of our patients, and we must go to the Orient or Central Africa to study these conditions uncomplicated by atherosclerosis. The speed with which renal failure develops after the acute inflammatory process is spent depends to a large degree on the rate at which atherosclerosis develops. This in turn depends on the degree of hypertension and alteration in plasma lipids. In the kidney, as in the retina, occlusive lesions of the main arterial trunks are rare, and disseminated sclerotic lesions, combining two or more of the types mentioned, affect the arterioles all the way into the glomerulus and, in diabetics with Kimmelstiel-Wilson syndrome, even into the glomerular capillaries.

In pyelonephritis the severity of disease may vary greatly from one lobule to another, but in other forms of Bright's disease a single needle biopsy of the cortex gives an excellent sample of the whole cortex.[4] Obtaining such samples involves less discomfort or risk than biopsy of the liver, so that the kidney can now be studied histologically and functionally more accurately and safely than any other organ save the skin. Our knowledge of the evolution of renal vascular disease and of its control by therapy is therefore certain to be more precise than that of other organs. Since its atheromatous lesions closely parallel those of the retina, careful study of either organ will enrich our understanding of disease in the other. This will be particularly valuable in following the effects of lowering arterial hypertension, since the role of elevated pressure in initiating or aggravating atherosclerosis is still disputed.

Because parenchymal atrophy and failing efficiency of enzyme systems occur in the renal tubules with aging even when vascular disease is minimal, the fixation of specific gravity of urine and decline in maximal rate of para-amino hippurate excretion with old age cannot be taken as accurate measures of functional impairment due to arteriosclerosis. Nor does the most precise study of urinary sediment provide decisive information on the relative importance of arteriosclerosis and of continuing glomerulitis in cases of chronic glomerulonephritis with hypertension. While the clinical management of these cases does not depend on such evaluations, there can be no doubt that understanding of the course of the disease in each individual will be enlarged by careful study of serial cortical biopsies.

HEART

The coronary system presents problems the reverse of those encountered in the previous sections. Arteriolar sclerosis is practically nonexistent even in malignant phases of hyperten-

sion. Inflammatory disease is a rare cause of internal thickening or thrombosis. Syphilis rarely extends beyond the ostia. Coronary atherosclerosis of the large branches lying in the epicardium is almost the only type of "arteriosclerotic heart disease," a term which should be abandoned and replaced by coronary sclerosis, coronary insufficiency or myocardial infarction. Even in the epicardial arteries the smaller branches are much less severely diseased than the main trunks.

Although coronary atherosclerosis and insufficiency are all too frequent, they have been blamed for many conditions for which they are not responsible. As in the brain, functional failure of the heart is often ascribed to vascular disease or to the myocardium outgrowing the coronary supply, when the real fault is an involutional or metabolic defect. The coronary blood flow studies of Bing[5,6] and Goodale[5] have confirmed the postmortem perfusion studies of Dock[7] and of Dresdale.[8] In cardiac hypertrophy and even in heart failure, blood flow per 100 gm. of ventricle per minute remains within the normal range; and if chronic anemia is present, the coronary flow, even in large failing hearts, may be far greater than normal, as is the perfusibility postmortem.[8] Insufficiency of coronary flow can be due only to coronary atherosclerosis, arteritis or embolism, or to low perfusion pressure. The latter occurs in the congenital displacement of coronary ostia into the pulmonary artery and in diastolic hypotension. When this is chronic, as in aortic insufficiency, coronary hyperplasia may provide normal coronary flow even for a greatly hypertrophied heart.[5]

When myocardial infarction strikes elderly subjects, congestive heart failure not infrequently occurs acutely or within a few months. Experience with infarction in young soldiers proved that heart failure was extremely rare, acutely or after recovery from large infarcts. In the heart, as in the brain and kidney, involutional changes prepare the way for organic failure with vascular accidents which, in young people, would be the cause of transient and trivial dysfunctions. Since the heart, like the brain, is subject to metabolic injury from poor diet, and this happens more often in poor old people than in others, what is called "arteriosclerotic disease" not infrequently proves to be greatly benefited by a diet adequate in protein and water-soluble vitamin, especially thiamine. "Arteriosclerotic," that is, coronary heart disease, can be evaluated only when anemia, Graves' disease and malnutrition have been corrected. Involutional change in myocardial function seems to be particularly susceptible to correction by digitalis which does not improve coronary flow, but an exact estimation of this element in heart failure can scarcely be made even after autopsy and the most meticulous clinical study.

Since atherosclerosis of the main coronary arteries may be advanced in normotensive young men who have no other visible atheromas, local factors, and notably the great thickness of the intima here as contrasted with the myocardial coronary twigs and other arteries of similar size, seem to be paramount. Without this, the metabolic disturbance shown by the plasma lipid pattern might only cause asymptomatic aortic lesions years or decades later. Family differences and even sex differences in the size, number and distribution of coronary intimal cushions at birth, and in the diffuse intimal thickening limited to the epicardial branches even in senescence, may explain some of the features of this form of atherosclerosis. Today this "middle-aged tax-payer's friend" has replaced pneumonia, the "old man's friend" in Sir William Osler's day, as Captain of the Men of Death.

The electrocardiograph, and more recently the ballistocardiograph, have been of great value in detecting and evaluating coronary disease after it has caused mild symptoms or even before symptoms have occurred. Figure 1 is based on data collected by Drs. H. and R. Mandelbaum on people free of symptoms and signs (including electrocardiographic changes) of cardiovascular disease. It shows how the incidence of ballistocardiographic abnormality in such subjects parallels the incidence of 3+ coronary sclerosis in a large series of miscellaneous autopsies. Starr[9] had already reported the high incidence of later coronary accidents among normal subjects with abnormal ballistic patterns. Such a method may help in selecting patients who might benefit from studies of plasma lipids and attempts at modifying abnormal patterns of lipid content of the blood.

LEGS

Vascular disease of the legs is far more striking in the veins than in the arteries but the latter show far more sclerosis than do the corresponding arteries in the arms and hands. The legs are colder, the arteries dilate less when metabolism

rises, and blushing stops above the waistline. While these facts may be related to crural susceptibility to both atherosclerosis and medial calcification, it seems probable that the greatest factor is a difference in arterial pressure. The pulse pressure and systolic pressure rise as the pulse wave goes down the aorta. Even in recumbency, pressure is higher in the legs than in the arms. Erect posture adds many centimeters of hydrostatic pressure (although never as much as the elevation of the heart above the vessel). Except in diabetics and a small group of heavy smokers, arteriosclerosis of the legs rarely causes symptoms before the age of fifty, but calcification in the femoral and tibial arteries may be demonstrated by x-ray for decades without symptoms. Presumably this is due to Mönckeberg's type of medial calcification which does not encroach on the lumen. Atherosclerosis involves both large and minute arteries in the legs, but arteriolar disease is limited to inflamed regions. These occur in a small percentage of heavy smokers, who have thromboangiitis obliterans, and also secondarily to varices or to chronic edema in heart disease and cirrhosis.

Although the hobbling gait of many old people shows that involution of joints and the nervous system has greatly increased the effort of walking, intermittent limp, like angina of effort, is due largely to vascular disease not involution. While angina is usually associated with pure atherosclerosis, intermittent limp is often a result of mixed vascular lesions. An effective method of controlling atherosclerosis probably would greatly reduce the vascular disease of the legs of diabetics but would still leave a group of patients with limp or gangrene due to angiitis and other vascular disorders.

FIG. 1. The crosses show the incidence of 3+ coronary disease disclosed at autopsy at the Mayo Clinic in a miscellaneous group of patients.[11] The black areas show percentage of maximal, the cross-hatched areas the percentage of marked, and the stippled areas the percentage of definite abnormality in ballistocardiograms of supposedly normal subjects (H. and R. Mandelbaum). The inflection on all curves in males at fifty-five years presumably is due to deaths from coronary disease exceeding rate of development of atheromas. The curves of severe and marked abnormality parallel the curves of incidence of coronary sclerosis although these are very different in men and women. The relatively great rise in minimal abnormality in older men and women probably is due to poor physical training and obesity.

AORTIC, ILIAC AND SPLANCHNIC ARTERIES

In the aortic, splenic, carotid and temporal arteries we can observe the most frequent form of arteriosclerosis, a form closely related to the venous involution which causes varices. This is called fibrosis with ectasia. Elastic and muscular elements atrophy, collagen increases and the loss of distensibility is compensated by dilatation and increase in length. The resulting tortuosity and the dilatation are evident on the temples of many men before they are thirty, and in the chest films of some middle-aged or aged people the aortic tortuosity and dilatation mimics that

due to syphilis. A striking difference is that secondary atherosclerosis and calcification, which often occurs in the ascending part of the aorta with syphilis, is rarely seen proximal to the aortic knob, on the descending limb of the arch, in the other group. In women, and in men with coarctation of the aorta, tortuosity of the common carotid or innominate arteries may also cause pseudo-aneurysms. In women, too, extreme tortuosity of the abdominal aorta is more frequent than in men. There is little evidence that these involutional changes greatly alter the rate of atherosclerosis or cause other vascular lesions or organic disease.

As men age, at least in North America, there is an increasing calcium content of the media, especially in the abdominal part of the aorta, but true medial sclerosis rarely involves the aorta, carotids or large splanchnic arteries. Cystic degeneration and necrosis, the precursor of sudden medial separation (dissecting aneurysm), also is a rare disorder, having a significant occurrence only in severe hypothyroidism combined with severe hypertension.

Atherosclerosis affects the arterioles of the adrenal glands, pancreas and, to a lesser degree, those of the gastrointestinal tract and liver only in severe hypertensive and diabetic vascular disease. Splenic arterioles also are affected and show intimal hyaline in many elderly people. But in the splanchnic bed the large arteries rarely show atherosclerosis comparable to that of the coronaries. This is nearly always associated with severe atherosclerotic ulceration and calcification of the aorta. In elderly patients, usually women, chronic post-prandial distress (abdominal angina) may be due to severe sclerosis of branches of the celiac axis. Occasionally fatal retroperitoneal hemorrhage occurs as a result of ulceration of abdominal aortic or iliac atheromas. Similar hemorrhages may also occur from rupture of aneurysms of renal arteries, especially on the right side. The differential diagnosis is important since surgical treatment is more likely to succeed with the renal arterial lesion. The use of roentgen-opaque media, injected by a needle inserted into the aorta through the left flank, may serve to demonstrate such aneurysms of the renal artery. In retroperitoneal hemorrhage from either type of lesion, pain and paralytic ileus are prominent features, and discoloration of the scrotum or vulva and abdominal wall may develop within a day.

GENERAL CONSIDERATION ON PATHOGENESIS AND CONTROL

It is now generally recognized that arteriosclerosis rarely causes trouble in normotensives before the age of fifty unless the heart or the legs are involved, and in such cases a disturbed cholesterol-phospholipid balance is usually demonstrable. As patients age the ratio of lesions in the brain and in the aorta rises and the cholesterol-phospholipid levels approximate those of people who have minimal sclerosis. Diet and defects of metabolism appear to be of much less significance in atherosclerosis manifest after sixty-five years of age than in that evident before fifty.

Excessive smoking has been noted in a higher percentage of those suffering coronary accidents before fifty than in control populations, and the reduced life expectancy of smokers established by Pearl must in large part be related to the very striking actions of nicotine on the cardiovascular system.[10] Ballistocardiographic changes equivalent to those of coronary disease occur in a few normal young smokers for many minutes after a cigarette, and seem to reveal poor habituation to tobacco. Severe electrocardiographic changes occur much more rarely from smoking. It may be safely stated that smoking is a definite factor in some cases of arteriosclerosis of the legs, probably contributes to coronary disease, and is almost a negligible factor in retinal, renal and cerebral arteriosclerosis. There is no evidence whatever that alcohol or any other agent abolishes the effect of smoking on the circulation.[10]

ARTERIOSCLEROSIS AND SMOKING

While there is a growing body of evidence that exogenous (dietary) cholesterol forms the bulk of the atheromatous deposits in cholesterol-fed rabbits,[10] and that dietary cholesterol as well as fat is a matter of some importance to individuals who develop coronary disease, there is far less evidence that smoking is an important factor in the rate of evolution of atheroma. This evidence has recently been summarized by Roth.[11]

The effects of tobacco are apparent as vasoconstriction in the extremities of all subjects, minor changes in the ballistocardiogram in one-third and in the electrocardiogram in one-half of normal subjects. Marked changes in the ballistocardiogram occur in over 5 per cent, in the electrocardiogram in less than 1 per cent. The cumulative effects of such changes probably contribute to the reduced life expectancy of

smokers reported by Pearl[12] but a far greater contribution to that mortality may be due to effects on the respiratory system. Not only cancer of the lung but chronic sinusitis, chronic bronchitis, emphysema and reduced resistance to pneumonic infection could be cited. Hence, while the physician can advise the inquiring patient with vascular disease of the leg that smoking will surely curtail blood flow in the diseased tissue, he cannot be dogmatic about the hazard to the patient with angina or coronary disease. Modern technics make possible detection of those whose cardiac function shows no disturbance and others who show striking deterioration. Objective proof of no effect is reassuring, and evidence of actual impairment of function due to half a cigarette may help a patient to give up this habit.

SUMMARY

Atherosclerotic accidents to the coronary circulation begin at an age when myocardial function is sound and in subjects of this age rarely cause heart failure. At older ages, however, the net effect of coronary disease and of myocardial involution is a steady rise in the incidence of heart failure with coronary atherosclerosis.

Arteriosclerotic accidents in the brain are infrequent prior to the age at which disseminated cortical atrophy, an involutional loss of neurones, usually begins to reduce mental acuity and memory. In nearly all cases in which personality changes follow cerebrovascular accidents involutional change is an important factor in reducing ability to resist injury. In some elderly subjects this is further complicated by inadequate supply of water soluble vitamins, including B_{12}, so that *a priori* assumption that all deterioration in mentation and emotional adjustment of oldsters is due to arteriosclerosis is not merely erroneous but harmful, since it eliminates from proper therapy many whose condition can be improved.

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Diet and Lipotropic Agents in Arteriosclerosis*

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THE use of low cholesterol diets and the administration of various lipotropic compounds are two types of therapy that have been advocated in recent years for the treatment of arteriosclerosis. This paper attempts to review the evidence for their value.

Both of these treatments are predicated upon the hypothesis that arteriosclerosis is due to a disorder of lipid metabolism which results in the deposition of lipids in the arterial wall as a principal factor in the formation of the lesion. The evidence for this hypothesis has been presented in prior articles in this symposium.[1–3] The low cholesterol diet is intended to cut down the supply of the most characteristic lipid of the lesion, while the use of lipotropic agents is directed at mobilization and removal of the lipids from the lesions. The two therapeutic measures can be evaluated on the basis of: (1) their theoretic mode of action, (2) their effects in experimental arteriosclerosis in animals and (3) a limited amount of data reported on their clinical application.

EFFECT OF LOW CHOLESTEROL DIETS

Theoretic Basis. The low cholesterol diet offhand seems a reasonable approach to prevention of cholesterol deposition in the arterial walls. Recent studies in cholesterol metabolism indicate, however, that a large amount of this substance is synthesized by the body from small molecules available from fat, protein or carbohydrate. Gould[2] has shown that dietary cholesterol depresses endogenous cholesterol synthesis in animals, a finding which may imply the converse, that if dietary intake is insufficient cholesterol synthesis will be increased. Although all three basic types of food can supply the small molecules for cholesterol synthesis, fats seem to be most efficiently converted and this provides a rationale for restriction of all fats as well as cholesterol in the dietary treatment of arteriosclerosis.

Animal Experiments. There is not much direct evidence from animal experiments for or against the low fat, low cholesterol diet. Horlick et al.[4] found that low fat diets did inhibit the spontaneous arteriosclerosis which occurs in chickens. Most experimental arteriosclerosis is produced in chickens, rabbits and dogs by feeding high cholesterol diets. This precludes studies of low fat, low cholesterol diet but can itself be taken as indirect support for the value of low cholesterol diets. It is also true that upon return to normal diets these animals all show regression of their arteriosclerotic lesions.[2,5,6] Equally indirect is the finding that inadequate caloric intake has an inhibiting effect upon the production of this type of experimental arteriosclerosis, possibly mediated by depletion of the pool of precursors for cholesterol synthesis.[7]

Clinical Studies. There is more support for low fat, low cholesterol diets from clinical studies. Thus statistical surveys of various segments of the population indicate that there is a higher incidence of arteriosclerosis in those groups whose diet is inherently richer in fats and cholesterol than in groups whose diets are poor in fats and cholesterol.[8–11] These studies, however, are open to criticism because the groups compared differ in other significant but uncontrolled factors such as heredity, nutritional status and differing age distribution. Nutritional status was studied by Wilens[8,12] in a series of autopsies. He found increased arteriosclerosis in obese individuals and less than the average incidence in

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people who were below average weight. Age has a recognized correlation with arteriosclerosis so that in groups in which life expectancy is low due to infectious diseases fewer individuals survive to the age at which arteriosclerosis becomes common.

More reliable data are available from studies of people experimentally placed on low cholesterol, low fat diets. Morrison[13] reported a direct influence of diet on arteriosclerosis in terms of diminished mortality in a group on a diet containing 25 gm. of fat as compared with a control group on a normal diet. Although his figures are statistically significant, the number of deaths involved is rather small and the work should be extended. There is also some question from the reports[14] as to whether these patients were not also receiving choline.

The ultimate in low cholesterol, low fat diets was used by Kempner[15] in his rice diet study. His diet contained no cholesterol and less than 5 per cent fat. Studying hypertensive cardiovascular disease principally, he found that in 363 patients with initial serum cholesterol levels over 220 mg. per cent there was an average drop of 74 mg. per cent after treatment with the rice diet; 148 patients with initial serum cholesterols below 220 mg. per cent showed an average decline of only 15 mg. per cent on the rice diet. Starke[16] subsequently presented data on 154 of Kempner's patients in greater detail, coming to the same conclusion. Watkin et al.[17] at this institution independently studied Kempner's rice diet and found that thirty-five of forty-one patients showed a lowering of serum cholesterol while on the rice diet, the average decline being 40 mg. per cent. Their data included the frequent cholesterol determinations necessary to average out random fluctuations. They also followed the weight of each patient, indicating that the observed fall in serum cholesterol was attributable to the qualitative nature of the diet and not to starvation. Mellinkoff, Machella and Reinhold[18] noted a fall in serum cholesterol averaging 85 mg. per cent in fourteen patients with intestinal disease when treated with a protein hydrolysate and dextri-maltose preparation that was low in fat. This fall they attributed to the low fat therapy but this is somewhat questionable due to the patients' underlying diseases. Hildreth, Malinkoff, Blair and Hildreth[19] have recently reported a closely controlled study of fat restriction in three healthy subjects. Reduction of the dietary fat from their normal levels of 97, 114 and 138 gm. to 9, 10 and 62 gm., respectively, in these three subjects caused serum cholesterol declines of about 45 mg. per cent in each case. Restoration of pure vegetable oil to the diets produced significant rises in the serum cholesterol levels, proving the necessity for fat as well as cholesterol restriction. Other studies of diet in relation to serum cholesterol level were made by Wilkinson, Blecha and Reimer[20] and by Gertler, Garn and White[21] in which a higher minimum level of fat and cholesterol intake existed and little or no apparent effect upon the serum cholesterol level was noted.

It, therefore, seems likely, as Keyes et al.[22] have pointed out, that the blood cholesterol level is independent of intake over a wide range of cholesterol in the diet but that as the intake approaches "zero," which they believe to be probably less than 200 mg. per day, the blood level does decline. It also seems established that to achieve significant lowering of serum cholesterol the diet must not only be extremely low in cholesterol but must also be restricted markedly in all fats. The addition of vegetable fat to such diets low in cholesterol results in a rise in the serum cholesterol level toward the pre-diet level. With really low cholesterol, low fat diets the serum cholesterol can be reduced by 40 to 80 mg. per cent in most patients and particularly in patients who have hypercholesterolemia. The ultimate value of this degree of serum cholesterol reduction in the therapy or prevention of arteriosclerosis remains to be determined.

In addition to studies on the effects of diet on arteriosclerosis mortality and serum cholesterol level, there is the work of Gofman et al.[23] on the quite striking influence of a low cholesterol, low fat diet upon the level of the S_f 12-20 lipoprotein fraction of serum. In a previous article in this series[3] Jones et al. described the correlation between the level of S_f 12-20 lipoprotein of human serum and arteriosclerosis. They found that a diet of less than 50 gm. of fat and 200 mg. cholesterol evoked a fall in the S_f 12-20 lipoprotein concentration in the serum of most patients. They reported that in fifty-six patients with S_f 12-20 concentrations above 80 mg. per cent, who were allegedly on this diet for a year after a myocardial infarction, there were no recurrent infarctions among the fourteen patients who showed a fall in their S_f 12-20 lipoproteins whereas sixteen recurrent infarctions occurred in the forty-two patients whose S_f 12-20

level remained above 80 mg. per cent. Unfortunately this study does not indicate the effect of the diet upon recurrent myocardial infarction directly since the authors used the trend of the S_f 12-20 level as their index of degree of adherence to the diet.

In contrast to Gofman's observations, a preliminary report of the S_f 10-20 lipoproteins of patients on the rice diet by Hatch and Kendall[24] states that this drastic diet resulted in substantial increases in the S_f 10-20 level in three patients, no change in three, and a decrease in only one. This is not discordant with Gofman's findings because the rice diet is much lower in fat than that studied by Gofman, and differs significantly in protein content as well. This rice diet effect is being studied further.

EFFECT OF LIPOTROPIC AGENTS

The case for or against the use of lipotropic agents in arteriosclerosis is much less clear and the available data are conflicting. Some of the conflicts are the result of inadequate knowledge at the time of early work and can now be resolved in the light of more recent findings. Some of the reports, however, seem to be based upon inadequate observations.

Theoretic Basis. The theoretic basis for the application of lipotropic agents to the management of arteriosclerosis is twofold, their lipotropic action and the fact that some are phospholipid components. Their use was suggested initially by the gross similarity of the fatty deposits in arteriosclerosis to those in fatty livers, which had just been reported responsive to substances now known as "lipotropic agents." This analogy is very superficial. The phrase "fatty liver" covers a number of different types of lipid infiltration of the liver arising from multiple causes. None of these lipid deposits are very similar chemically or histologically to the lesions of arteriosclerosis. This reasoning by analogy is even more faulty because the lipotropic agents are not uniformly effective against all fatty livers. Some types of fatty liver respond, others do not.

The lipotropic agents comprise five chemical compounds: choline, methionine, betaine, inositol and β-propiothetin.[25] The last can be dismissed in that it is thus far known to occur in seaweed, is unstudied in foods, and has not been applied to arteriosclerosis. The first three are interrelated in that methionine and betaine act by providing labile methyl groups for the synthesis of choline.[26] Chemically, inositol stands in a class by itself, apparently unrelated to choline. A number of more complex substances have lipotropic activity by virtue of their choline content or their ready conversion to this compound. Thus lecithins, for example those derived from soy beans or egg yolk, yield choline upon hydrolysis. Proteins are lipotropic due to their methionine content, which in turn gives rise to choline. Lipocaic from pancreas is still too indeterminate for consideration.[27] This leaves just two compounds to be evaluated, choline and inositol.

Choline was the first compound shown to have lipotropic activity. This was accomplished by Best in 1932[28] when he recognized it as the active component in lecithin. It is effective in removing fat from livers made fatty by choline deficient diets or by high fat diets but not from fatty livers produced by carbon tetrachloride or phosphorus.[29] It is therefore not a universally effective lipotropic agent for fatty livers, to say nothing of arteries. Gavin and McHenry reported a curative action of inositol upon fatty livers arising from high fat diets.[30] There is still some controversy over its general effectiveness and whether it does anything that choline does not.[31,32] Initially, it was believed to have some specificity for the cholesterol type of fatty liver but Best[25,32] recently has evaluated it carefully and now believes that inositol does nothing that choline will not do except in very short (less than two weeks) experiments. It is not as strongly lipotropic in maximally effective doses, and is completely ineffective if fat is present to the extent of over 2 per cent in the diet. Most of the confusion in the past was apparently due to chance biologic variation when small numbers of animals were used, and to different effects dependent upon the duration of experiments and variation in the diets used by several investigators. In general, the specificity of action of lipotropic compounds for certain types of fatty livers and the conditions necessary for demonstration of their activity even in livers leave little theoretic basis for their use in the prevention or treatment of arteriosclerosis.

The second theoretic basis for the use of choline in arteriosclerosis came later when the probable importance of the phospholipids in the pathogenesis of the disease became apparent.[2] There is increasing evidence to indicate that the ratio of serum phospholipids to serum cholesterol may be more important than the

level of the serum cholesterol alone. If the serum phospholipids are involved in the prevention of arteriosclerosis, certainly choline and possibly inositol might act favorably by providing components of the phospholipids and thereby contributing to a desirable high level of these lipids. There is in this a reasonable rationale for testing these substances in the therapy or prophylaxis of arteriosclerosis, regardless of any consideration of lipotropic activity demonstrable in the liver.

Animal Experiments. Quite a large number of studies have been made of the effects of various lipotropic agents upon experimental arteriosclerosis in animals, since in such experiments it is possible to determine the degree of arteriosclerosis at autopsy as well as to study the effect on serum cholesterol levels. Rabbits, chickens and dogs have been used, the majority of published reports relating to rabbit experiments. With both rabbits and chickens there have been conflicting conclusions as to the effectiveness of the substances tested. The number of reports in favor of the lipotropic agents exceeds the unfavorable reports but this is a misleading index of results because of the reluctance and lack of interest of many investigators in publishing their negative experiments. Critical analysis of the published reports reveals that many of them must be rejected as inconclusive for various reasons.

Experimental arteriosclerosis, as produced in rabbits by cholesterol feeding, is subject to a large number of factors which influence the incidence and severity of the lesions. It is now recognized that even with all known variables controlled there is such marked biologic variation in experimental arteriosclerosis in rabbits that it is hazardous to use less than about twenty animals for each test regimen, with an equal number of control experiments limited to feeding the same quantity of cholesterol alone.[33] In setting up an experiment the control and test groups should be of identical strain, sex distribution, age and weight. They should be carried on experiment simultaneously for the same length of time. Frequent serum cholesterol determinations should be made and the rates of weight gain should be followed. Neglect of any one of these requirements in the evaluation of a drug in the prevention or cure of experimental arteriosclerosis in rabbits leaves the results of the experiment open to question. The requirements of strain or heredity control is fundamental. Age has been shown[34,35] to be an important factor in determining the ease with which arteriosclerosis can be produced in rabbits. Sex has been noted to play a role in that some male rabbits seem to be rather refractory to the development of hypercholesterolemia and arteriosclerosis on this regimen.[36] The initial weight and the rate of weight gain during the experiment are recognized as having an appreciable influence upon the arteriosclerosis.[7,37] The thriving, weight-gaining rabbits seem to develop more arterial lesions than their lean brethren. The necessity for simultaneous controls cannot be emphasized too strongly, a requirement that is frequently neglected because it requires more in the way of facilities and personnel. There is also the temptation to use a single control group for comparison with several successive test groups. In our own laboratory we have seen strictly comparable control groups of rabbits in successive years show significant differences in the incidence and severity of arteriosclerosis. This is most pronounced if the seasons happen to differ, because rabbits do not do well in summer. Contemporary controls in the same animal quarters also serve as a check on such intangible variables as differences in commercial food lots and unrecognized intercurrent disease in the rabbit colony. These can inhibit the development of arteriosclerosis. Frequent serum cholesterol determinations serve to check the comparability of the control and test animals (when the test substance is to be used in a curative experiment), or to reflect possible effects of the test substance upon the serum cholesterol (in the preventative type experiment). This latter use of cholesterol levels is hazardous because mere acceleration of the dietary cholesterol through the gastrointestinal tract by an irritative effect of the test substance can probably result in lower values. Finally, if all of these conditions have been complied with to achieve the ideally controlled experiment, at the end of such an experiment it usually is impracticable to perform the minimum of twenty control and twenty test animal autopsies within an insignificant interval of time.

As a result of all these difficulties compromises have been made by all investigators with resultant invalidation of many of the experiments. Moreover, if a test group showed less arteriosclerosis than the control group, the test agent was likely to become the subject of a published report; if there was no difference between the

groups, the investigator was generally inclined to dismiss the experiment as inconclusive. Custom seems to require much better data for negative reports than for positive ones.

Most of what has been said of the design and interpretation of rabbit experiments applies in general to chicken and dog studies. Rodbard et al.[38] have shown that age and season of the year profoundly influence the development of arteriosclerosis in chickens. Birds on a uniform regimen show progressive development of arteriosclerosis from the eighth to the twentieth week of age, but after twenty weeks the arteriosclerosis slows down and may even regress. Studies on birds under eight weeks of age showed that arteriosclerosis could be produced in the winter season but not during the summer. In both chickens and dogs spontaneous arteriosclerosis occurs with old age. Thus 50 per cent of chickens have arteriosclerosis at the age of one and one-half years,[4] and Bevans has found arteriosclerosis in all of twenty-seven dogs between nine and nineteen years of age.[39] Katz and co-workers have favored the use of young chickens, large numbers of which can be conveniently used to cancel out biologic variations. Kendall and his group have used dogs because they believe that the experimental canine disease is more closely analogous to human arteriosclerosis and that there is less variation in the dog than in the rabbit.

Most of the experiments cited by pharmaceutical firms in support of the use of lipotropic agents in arteriosclerosis are open to criticism on one or more of the above counts. When the literature is reviewed with these requirements for adequately controlled experiments in mind, there are only a few that escape rejection. In general, the results of even these experiments are suggestive rather than conclusive.

Steiner[36] in 1938 reported that choline administered to nineteen six-months-old male rabbits on a high cholesterol diet over periods of 40 to 100 days resulted in only nine grossly arteriosclerotic animals, compared with fifteen diseased animals in the group of nineteen control rabbits on the same regimen without added choline. He stated that "on a statistical basis the results are not striking," and concluded that "choline delays, but does not prevent, arteriosclerosis in cholesterol-fed rabbits." That same year Steiner[40] reported a curative type of experiment in which twenty six-month-old male rabbits were fed cholesterol for 110 days. This lot of arteriosclerotic animals was then divided into three groups. Five rabbits were sacrificed at once; the remainder were placed on plain food without cholesterol for sixty more days with ten of the latter receiving 0.5 gm. of choline daily. At the end of the experimental period all rabbits were sacrificed. The incidence of arteriosclerosis in the first five rabbits sacrificed at the end of the cholesterol feeding was the same as in the five which were on plain food alone for sixty more days, and both of these groups showed a higher incidence of arteriosclerosis than the remaining ten rabbits which had received choline. The number of animals used in these experiments was small and the serum cholesterol levels of the group which served as controls were somewhat higher than those of the choline group. In the same year Himsworth[41] studied the effects of choline in cholesterol-fed rabbits. He used littermate five to six month old animals divided into six groups with too few animals per group to permit any conclusions. He believed, however, that choline was without any effect upon the arteriosclerosis. A quite similar experiment was carried out by Baumann and Rusch[42] that year with the same conclusions, but again based on two experiments each involving only twelve rabbits which were divided into three groups. Cholesterol levels were controlled but the animals varied too much in weight and were too few per group to be conclusive. The Keston and Silbowitz study[43] in 1942 of soya lecithin and choline in rabbits fed cholesterol involved only seven or eight rabbits per group, and included no mention of any serum cholesterol levels. Their control group of eight rabbits showed arteriosclerosis in seven, while three test groups of seven, eight and eight on lecithin or choline showed two, two and three diseased animals, respectively. These earlier experiments were all of a pilot nature and, in the light of what has since become known about factors influencing experimental arteriosclerosis in rabbits, were inadequately controlled.

More recently several studies of choline in rabbits have reported it to be effective against experimental arteriosclerosis. Morrison[44,45] investigated the prevention of arteriosclerosis in cholesterol-fed rabbits. He reported an incidence of 75 per cent moderately severe (+++) to marked (++++) arteriosclerosis, with 5 per cent of animals free of lesions in his twenty control rabbits after ninety-two days on the diet. Twenty-nine similar animals which received

0.5 gm. choline hydrochloride per day in addition to the diet showed not even moderately severe (+++) arteriosclerosis, and 55 per cent were entirely free of lesions. On twice this choline dosage 78 per cent of the thirty-two rabbits were free of lesions. These figures are impressive but there is no mention of serum cholesterol levels and no statement as to whether the test and control animals were run simultaneously. If these two variables were not controlled, the observed differences could well have arisen through either of these important factors. Morrison[45] further reported a curative type of experiment in which arteriosclerosis was produced in forty-four rabbits by cholesterol feeding for 184 days. The rabbits were then divided and half got plain food alone as controls, while the other half received plain food plus choline for the next 185 days. In the twenty-one surviving control rabbits there were none free of arteriosclerosis. Of the twenty-two choline-treated animals 74 per cent were free of lesions. Again there were no serum cholesterols or weights mentioned to assure comparability of the two groups, and it is not stated that they were run simultaneously. Broun et al.,[34] using a total of 224 cholesterol-fed rabbits, fed groups of six to eighteen animals choline, betaine, methionine and inositol at various dosage levels. Some groups of rabbits were three months old, others six to eight months old. The eighteen rabbits on 40 to 160 mg. per day of betaine showed no effect of the medication. Similarly, 40 mg. of methionine and 40 mg. of inositol in groups of six rabbits each were inactive. In the case of choline, 40 mg. per day (the largest dose) did nothing in the six to eight month old rabbits, but in thirty month old rabbits doses from 2 to 500 mg. of choline were tested and the doses of 75 mg. per day and up seemed to inhibit the production of arteriosclerosis. This might have been due to depression of appetite by the choline but the authors reported that the various groups of animals showed "little difference in weight gain." These three month old rabbits showed serum cholesterol levels of only 400 to 700 mg. per cent as compared with several times this level in the older animals, so this might be a partial choline effect which can be overcome by greater hypercholesterolemia. The choline doses reported as effective are in line with those that have been generally used by other investigators. It is most interesting that when the regular diet was supplemented with 1 gm. of Crisco per day the maximum 200 mg. of choline per day lost its effectiveness in protecting the animals against arteriosclerosis. This suggests that the basic diet in these experiments might have been unusually low in fat or deficient in choline. Steiner[46] has repeated and extended his earlier work on choline in rabbits. This time twenty-five controls received a high cholesterol diet alone and twenty-nine rabbits got this plus choline hydrochloride at two dosage levels, 500 mg. per day for eighteen animals and 1.0 gm. per day for eleven animals. Animals were sacrificed in pairs from each group (four animals) at intervals of five to ten days between the 40th and the 100th day of the experiment. None of the choline-treated animals sacrificed between the 40th and the 80th day showed arteriosclerosis, while ten of eleven control rabbits showed lesions at the end of the same period. The serum cholesterol levels of the two groups were quite similar but a little lower in the control group. No data were given as to the weights of the animals so there was no quantitative control on the relative rates of gain in the control and test groups. Recently this has been claimed to have a significant effect in rabbit arteriosclerosis[7] and could readily be a factor when the diet of one group is flavored by choline.

These conflicting past reports on the effect of lipotropic agents upon experimental arteriosclerosis in rabbits have stimulated several carefully controlled studies recently. Meyer et al., in an unpublished experiment,[47] studied choline for possible curative action. Arteriosclerosis was produced in forty-three chinchilla rabbits by cholesterol feeding for 107 days. Serum cholesterol determination were obtained every two weeks and the figures averaged to yield a mean serum cholesterol level for the entire 107-day period for each animal. On the basis of these cholesterol averages the rabbits were then divided into three groups, matched in their distribution of mean serum cholesterol levels and therefore as comparable as possible in the incidence and severity of their arteriosclerosis. Group A, containing thirteen rabbits, was sacrificed at once to determine the degree of arteriosclerosis in this representative sample of the colony. The average of the mean serum cholesterol levels in this group was 1005 mg. per cent. Autopsies were performed and the arteriosclerosis found was graded on a scale of 0 to 4+ in (1) the ascending aorta, (2) the thoracic aorta, (3) the abdominal aorta and (4)

the pulmonary artery. As an additional index of the severity of the lesions, chemical analyses were made of each individual aortic intima and media for its content of various lipids. The remaining two groups of rabbits were continued on experiment. Group B, containing fourteen animals with an average mean serum cholesterol level of 1068 mg. per cent, was placed on a plain stock diet as controls against further changes in the lesions. Group C, containing twelve rabbits with an average mean serum cholesterol level of 1067 mg. per cent, was placed on the same plain stock diet with 1 gm. of choline hydrochloride in aqueous solution mixed with a small first portion of each rabbit's daily food. This technic assured consumption of the choline without having the rabbits' entire diet flavored by the choline. After 112 days on their respective regimens the rabbits in groups B and C were sacrificed and studied in the same manner as group A. The results in terms of averages for each group of rabbits are given in Table I. It should be noted that rabbits in groups B and C remained hypercholesterolemic during the regression period of the experiment despite no cholesterol intake. The arteriosclerosis in these groups was accordingly more severe than in group A. This rabbit experiment gave no evidence of any effect of choline upon the experimental arteriosclerosis. A similar failure to demonstrate effects of choline on regression of arteriosclerosis in rabbits (in unpublished experiments) was mentioned by Duff.[1]

Moses and Longabaugh[37] have reported quite a similar cholesterol-fed rabbit experiment designed to study the effect of choline in prevention of arteriosclerosis. The animals were all males from a single colony and between ten and twelve months of age. Serum cholesterol levels were determined weekly and each rabbit was weighed twice a week. Three groups of ten rabbits each were used and all were fed the same high cholesterol diet. One group received nothing else and served as controls. Group two had 1 gm. of choline salt mixed with the food of each rabbit daily. Group three similarly received choline but in doses of 4 gm. per day per rabbit. After six weeks on the experimental diets all animals were sacrificed and examined. Addition of the grades of arteriosclerosis in the animals in each group showed a score of 24 for the controls, 19 for the second group (on 1 gm. choline) and 26 for the third group (on 4 gm. choline). These figures fail to show an influence of choline upon the lesions. Despite this, there was one animal free of lesions in group one, as opposed to two in group two and three in group three. This might be interpreted as indicative of a protective effect of choline but is offset by a higher incidence of very severe arteriosclerosis in the choline-fed animals plus the fact that the average weight gain in the five test animals free of lesions was 12 gm. as opposed to an average gain of 416 gm. in the entire control group. This was a well controlled experiment but is marred by the marked biologic variation in the small numbers of animals in each group and the observed lower weight gain in the choline-fed animals, a complicating factor which could inhibit arteriosclerosis. Both factors

TABLE I

	Average Serum Cholesterol mg. % during:		Gross Pathology Atherosclerotic Involvement (Scale of 0–4+)				Analysis of Aortic Intima and Media Lipids (gm./100 gm. Dry Wt.)						
	Cholesterol Feeding Period	Regression Period	Ascending Arch of Aorta	Thoracic Aorta	Abdominal Aorta	Pulmonary Artery	Dry Wt. gm.	Cholesterol			Phospho Lipid (Lipid P × 25)	Total Lipid	Neutral Fat
								Total	Free	Ester			
A	1005	...	3.1	1.7	1.7	2.8	0.220	2.52	1.20	1.32	2.97	23.4	16.9
B	1068	600	3.7	2.4	2.0	2.6	0.176	10.10	4.08	6.02	4.55	25.6	6.4
C	1067	646	3.7	2.5	2.3	2.6	0.166	11.88	5.07	6.81	5.63	28.7	6.2

make it impossible to conclude that choline had any unequivocal influence upon the arteriosclerosis.

The effect of inositol has recently been studied in rabbits in two unpublished experiments. Ellenbogen and Kendall[48] used twenty-eight rabbits of the same stock. These were divided into four groups of matching body weights. Two groups were controls on stock diet and stock diet plus inositol, respectively. The third group was fed a high cholesterol diet alone, while the fourth group received the high cholesterol diet plus 0.5 gm. inositol six days a week. In all animals the serum cholesterol and phospholipids were followed and the gain in weight was measured. The animals were on experiment simultaneously in the same animal quarters. All animals were sacrificed and examined after eighty-four days. The results are given in Table II. This experiment was well controlled but suffered from the compromise made in using too few rabbits. There is, however, no indication that inositol had any effect upon the serum lipid levels, the amount of fat deposited in the liver, or the amount of arteriosclerosis produced. The second inositol study was carried out by Moses.[49] Though designed completely independently of Ellenbogen et al. it followed strikingly parallel lines. Moses used all male albino rabbits. He simultaneously had seven rabbits on cholesterol diet alone, nine on cholesterol diet plus 2 gm. inositol per rabbit daily, and nine on plain food plus 2 gm. inositol per rabbit daily. Weight gain and serum cholesterol levels were determined and were strictly comparable in the two cholesterol-fed groups. The third group on inositol without cholesterol gained less and had normal serum cholesterol levels, as would be expected. When the animals were examined after twelve weeks on their diets, the grade of arteriosclerosis (on a 0 to 4+ scale) in the cholesterol-without-inositol group averaged 2.6+; in the cholesterol-plus-inositol group 3.7+; and in the inositol-without-cholesterol group 0.0+. There was no evidence of any inositol effect but the numbers of animals were small so Moses did a second experiment. This time three groups of twenty-six comparable rabbits were used. Each group was fed a different level of cholesterol in its diet. Of each twenty-six, eight received no inositol and served as controls, while the remaining eighteen in cages of six were given 4, 8 and 12 gm. of inositol per cage in their drinking water daily. This division of animals permitted the study of a range of inositol dosage in rabbits under various dietary cholesterol loads. Serum cholesterol levels and the weights of the animals were followed and there was no evidence of any effect of inositol upon these measurements. Two animals from each of the twelve groups on different regimens were sacrificed after four, six and eight weeks on experiment. This added various time intervals to the already different regimens. The arteriosclerosis in the inositol-fed rabbits was in all instances comparable to that found in the corresponding control animals. In this experiment inositol was studied over a range of dosages and under different conditions of time and cholesterol feeding. This reduced the number of animals per subgroup to only two or four, numbers too small to be significant if a group differed from the bulk of the data. Since there was no such deviation of any of the groups, the

TABLE II

Regimen	No. of Rabbits	Average Serum Levels			Wt. Gain (gm.)	Estimated Degree (Scale of 0–4+)	
		Cholesterol (mg. %)	Lipid Phosphorus (mg. %)	Moles Chol./Phos.		Arteriosclerosis	Fatty Liver
Stock diet	7	56	4	1.1	625	0	0
Stock diet + 3 gm. inositol per week	7	45	4	1.0	570	0	0
Cholesterol-containing diet	7	667	12	4.6	550	1+, 1+, 1+, 1+, 1+, 2+, 2+	1+, 1+, 2+, 2+, 3+, 4+, 4+
Cholesterol-containing diet + 3 gm. inositol per week	6	781	13	4.7	635	1+, 2+, 2+, 2+, 3+, 3+,	2+, 3+, 3+, 3+, 3+, 4+

experiment as a whole seems highly significant and provides rather convincing evidence that inositol has no influence upon the development of arteriosclerosis under these conditions.

Another unpublished study of lipotropic agents in cholesterol-fed rabbits has been made by Kellner.[50] Soya lecithin preparations containing both choline and inositol were employed. He used approximately 100 rabbits divided into experimental groups of ten and twelve. Some were maintained on plain food, some on plain food plus lecithin, some on a cholesterol-containing diet alone, and some on this last diet plus lecithin. The doses of lecithin were calculated to be proportional to the doses recommended by the manufacturer for use in human subjects. All animals were followed as to weight and both serum cholesterol and phospholipid levels. Kellner found that lecithin caused no change in the serum phospholipid levels in the animals on plain food. In the cholesterol-fed rabbits there was no difference between the controls and the lecithin-treated groups in regard to serum cholesterol-to-phospholipid ratios or in the resultant arteriosclerosis.

Evaluation of the lipotropic agents in arteriosclerosis in chickens has been reported frequently by Herrmann[51–54] and by Stamler et al.[55,56] The former believes that the lipotropic agents are effective while the latter has been unable to demonstrate any favorable action.

Herrmann used old hens as his experimental bird, because of their high incidence of spontaneous arteriosclerosis. He followed the blood and tissue cholesterol concentrations as indices of the efficacy of the drugs. He fed choline,[51] methionine[53] and inositol[52] in efforts to reduce the blood cholesterol levels. All of these agents produced statistically significant blood cholesterol reductions in apparently adequate numbers of birds as compared with control bleedings in the same birds. Upon analysis of the heart, aorta and liver of the treated and simultaneous control hens there was significantly less cholesterol found in the organs of the treated hens. The experimental data appear to justify Herrmann's conclusions that choline, methionine and inositol did reduce the blood cholesterol level and diminish the tissue cholesterol content in his old hens. The significance of these findings with regard to arteriosclerosis is chiefly inferential. No report has been made of the direct effect of the lipotropic agents upon the arteriosclerotic lesions.

Stamler et al. studied the effect of choline and inositol upon the development of arteriosclerotic lesions in young chicks. The lesions studied were of three types: those induced by cholesterol feeding,[56] those induced by stilbestrol[55] and spontaneously occurring lesions.[55] In the cholesterol-induced arteriosclerosis experiment ninety-six birds were divided into six groups of twelve test birds each and one control group of twenty-four birds. All ninety-six birds were fed the same basic diet but one pair of test groups was given 0.25 per cent cholesterol in their diet; a second pair, 0.5 per cent cholesterol; and the third pair 2.0 per cent cholesterol. One of each pair of groups on a given diet was also given a combination of 1 per cent choline and 1 per cent inositol in its particular cholesterol-enriched diet. All birds were weighed weekly, food intake was recorded and bloods were drawn at intervals for complete serum lipid fractionation. Birds from test and control groups were sacrificed at intervals after fifteen to forty-seven weeks of experimental feeding. Under these conditions choline and inositol had no prophylactic effect against hypercholesterolemia, hyperlipemia, aortic lipidosis or atherosclerosis. On the contrary, the lipotropic factors tended to aggravate both the hyperlipemia and the atherosclerosis. In the stilbestrol-induced arteriosclerosis experiment twenty-four birds were implanted with stilbestrol pellets and twelve of these served as controls on regular diet while twelve were fed the same diet containing 1 per cent choline and 1 per cent inositol. The conduct of the experiment was the same as in the case of the study of cholesterol-fed birds. There was no evidence of any effect of the lipotropic agents upon blood or tissue lipids or the arteriosclerosis. The study of spontaneous arteriosclerosis was carried out in an analogous manner with forty-eight birds. Half were on regular diet and half on the lipotropic diet. The results were completely negative. These experiments differ in many ways from those of Herrmann but seem to bear more directly on the problem. They showed no evidence of any inhibitory action of choline and inositol upon arteriosclerosis in chicks.

The influence of choline and inositol upon the development and regression of experimental arteriosclerosis in the dog has been investigated by Kendall and co-workers.[57] Experimental arteriosclerosis can be produced in dogs by feeding cholesterol and thiouracil.[58–60] The experimental canine arterial lesions seem mor-

phologically and anatomically more similar to human arteriosclerosis than either the rabbit or chicken lesions. This as well as the fact that the dog is omnivorous like man has made our group favor this experimental animal. Choline was studied first and was tested for a possible inhibitory effect upon the production of arteriosclerosis.[57] In a pilot experiment three dogs were fed cholesterol, thiouracil and 5 gm. of choline hydrochloride per day for fourteen months. Their hypercholesterolemia was comparable to what had been observed previously in five dogs on the same regimen without choline. At autopsy all three animals had extensive gross arteriosclerosis. A better controlled experiment was then performed. Fourteen mongrel dogs were started on experiment at four months of age and fed a 5 per cent cholesterol diet ad libitum. The dogs were individually given 0.6 gm. thiouracil daily. Eight of the dogs were maintained on this regimen as controls while six were given choline hydrochloride mixed with their food in an amount equal to 2.5 per cent of the diet. Serum cholesterol determinations were made in all dogs every two weeks and four to seven of the samples of serum from each dog were also analyzed for phospholipid content. All of the choline-fed dogs were on experiment at the same time but only four of the control dogs were on experiment concurrently with them. After four months on the experiment all dogs were sacrificed and examined. It was not possible to demonstrate any effect of the choline upon the treated dogs as compared with the controls in respect to serum levels of cholesterol or phospholipids, in degree of fatty infiltration of the liver, or in the extent and severity of the arteriosclerosis which was present in all animals. In a subsequent unpublished experiment[61] choline was studied for possible curative effects. Arteriosclerosis was produced in six dogs by cholesterol and thiouracil feeding for six months. The dogs were then taken off this regimen and placed on plain food for four months. Under these conditions the arterial lesions are known to regress.[5] During this last four-month regression period 2½ per cent choline hydrochloride was added to the plain diet. At the end of the regression period the extent of the arterial lesions in these six choline-treated animals was compared with that in nine dogs observed after being placed on the same experimental regimen without added choline. The controls were not all run concurrently with the test dogs. There was no difference between the two groups of dogs when animals of similar degree of effective hypercholesterolemia were compared.

Inositol was studied in ten dogs in the preventative type of experiment with no apparent effect of the drug on the serum lipids or the resultant arteriosclerosis, as compared with fifteen control dogs. The inositol dosage was 3 gm. per dog per day. The effect of inositol upon the regression of arteriosclerosis in dogs is currently being investigated.

In summary, the data on studies of the value of lipotropic agents in arteriosclerosis in experimental animals are conflicting. It does seem, however, that the more recent and better controlled studies of the action of inositol and choline in both rabbits and chickens have not demonstrated any effect of these agents either in preventing or curing arteriosclerosis, or in influencing the serum lipid pattern in what would seem to be a favorable manner. Only our own group has studied these agents in the dog but no beneficial effects have been demonstrated in this species.

Clinical Studies. Very few clinical studies of the effects of lipotropic agents upon human arteriosclerosis have been reported despite wide use of these compounds in medical practice. Controlled clinical studies are difficult because of the chronicity and marked variability of the disease. The diagnosis of arteriosclerosis is most secure in patients who have had a myocardial infarction so these are the patients in whom the drugs can best be evaluated. If evaluation is to be direct, the patients have to be followed while on the medication until sufficient numbers of deaths or complications from arteriosclerosis have arisen in comparable series of treated and control patients. This requires large numbers of patients and many years of observation. Throughout this period there is always the danger that the patients on the drug may get more careful medical attention than the controls and that thereby factors other than the drug under test may favorably influence the test patients' course.

One such "direct" study has been reported by Morrison and Gonzales in several articles.[14,62–64] They used "alternate unselected patients" who survived proven coronary thromboses as their control and test groups. There were 115 patients in each group, with the sex, age and hypertension distributions reported comparable. The test group was given choline

in doses of 6 to 32 gm. per day, the average dose being 12 gm. These patients were then followed for periods up to three years and the mortality tabulated. There were thirty-five deaths in the control group and fourteen in the treated group. These figures are significantly different statistically and remain so upon breakdown into the deaths from recurrent coronary thrombosis (19 vs. 6), cardiac failure (10 vs. 5) and noncardiac causes (6 vs. 3). This last category raises the question as to whether greater medical care for the patients given choline may not have influenced the results. The authors have not made this point entirely clear and there seems to be no specific accounting for individuals in this study of 230 patients who must have been lost to follow-up. A completely satisfactory experiment of this type should utilize placebo medication in the control group.

Less difficult indirect studies of lipotropic agents for human arteriosclerosis have been made by using the level of the serum cholesterol and serum phospholipids as indices of the possible action of the drugs. As with animals, this index is probably valid. In this type of experiment the chief pitfalls are the marked spontaneous fluctuation of the serum cholesterol level in patients with arteriosclerosis[65,66] and the fact that weight loss can cause reduction of the serum cholesterol level.[67] The latter is emphasized because both choline and inositol in doses that have been used can cause gastroenteritis and anorexia with possible resultant weight loss.

Soya lecithin was studied by Steiner and Domanski[68] in six patients with coronary arteriosclerosis and two patients with rheumatoid arthritis. A reduction of serum cholesterol was observed in all patients, with no difference between the two types of patients. The average maximum serum cholesterol decline was 68 mg. per cent. The decline, however, was maintained for only five weeks after which the serum cholesterol rose again despite continued soya lecithin feeding. Sufficiently frequent and numerous serum cholesterol determinations were made but there was no report of the weights of the patients. A fall in weight upon initiation of the lecithin feeding with later adaptation to the regimen and maintenance of weight could account for the findings in this experiment.

Herrmann has published several reports of studies of the effects of choline, methionine and inositol upon the serum lipid levels in humans.[54,69,70] He gave choline in doses of 1 gm. three times a day to forty patients for periods of one and one-fourth to three and three-fourths months and observed an average reduction of 20 per cent in the total serum cholesterol. In the case of 0.5 gm. methionine given three times daily for two to four weeks to six patients, the reduction was reported as 10 to 15 per cent, with one patient showing a 33 per cent increase. In twenty patients given 0.5 gm. of inositol four times a day for twenty-five to thirty days there was a 19 per cent average reduction of serum cholesterol level. In all of these reports there is no mention of what happened to the weights of the patients or any record of the number of baseline serum cholesterol levels made in each patient to evaluate random fluctuation. The number of patients in these studies was generally too small to permit any definite conclusions. More recently Herrmann[74] has reported on larger numbers of patients on choline and on inositol regimens. Only average figures are given for the serum cholesterol levels before and after treatment. The serum cholesterol reductions produced amounted to 10 to 20 per cent of the initial levels. Similar studies on soya lecithin showed no significant reduction.

Morrison[71] attempted to study the effects of choline on the serum cholesterol levels of forty-eight patients who had had recent coronary thromboses. He reported that in these patients given 6 gm. of choline per day there were such marked fluctuations of the serum cholesterol level that it was impossible to determine whether a reduction or an increase predominated. In contrast to these arteriosclerotic patients a small group of normal people fed choline by Paul, Daum and Kemp[72] showed very little variation in their serum cholesterol levels, with as many showing a rise as a fall.

Inositol has been studied in diabetics by Felch.[73] A group of thirty diabetics selected for hypercholesterolemia and stability of their diabetes were fed 3 gm. of inositol daily for eight weeks. Serum cholesterol and lipid phosphorus determination were made two or more times before the start of inositol and after one, two, four and eight weeks on the drug. Both lipids were found to fall appreciably while the patients were on inositol. In this study variations in the degree of control of the diabetes alone could have accounted for the results. This possibility is further suggested by the fact that the lipids returned only part way to their baseline levels while the patients were followed for six weeks after inositol was discontinued. Unless

placebo medication is used in a control study in a group such as this greater medical attention during the trial of the drug may inadvertently result in more strict adherence to diet, with consequent better regulation of the diabetes and a favorable effect upon the blood lipid levels.

In all of these clinical studies, as in the animal studies, it is always difficult to be certain that reductions in serum cholesterol levels upon administration of lipotropic agents are not due to secondary factors such as weight loss. This is very likely to occur when choline or inositol are fed, due to production of anorexia and diarrhea by these compounds.

CONCLUSIONS

Under certain circumstances low cholesterol, low fat diets are capable of lowering the levels of serum cholesterol. The degree of dietary lipid restriction necessary to achieve this effect in some patients may preclude the use of this regimen. It is not established that the maximum depression of serum cholesterol level obtainable by dietary measures will affect arteriosclerosis in man. Evidence in the experimental animal, however, suggests that a restricted lipid intake produces regression of experimentally induced arteriosclerotic lesions.

Consideration of all data available to date indicates that despite individual positive reports there is no general agreement that choline or inositol have any specific influence upon arteriosclerosis or the serum cholesterol level in man or the experimental animal.

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Conference on Therapy

Use of Curare and Curare-like Agents

THESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. GEORGE READER: This therapy conference will be on the use of curare and curare-like agents. Dr. Wescoe and Dr. Riker, who have studied the pharmacology of these drugs, are here. Dr. Wescoe will open the discussion.

DR. W. CLARKE WESCOE: Curare, as you all know, is a very old drug with a fascinating history. Its medical usage has largely been confined to the last sixteen years. Prior to that time only understandardized crude preparations of curare were available and the results obtainable from its use were equally crude and unpredictable. In 1935 the active principle, *d*-tubocurarine chloride, was isolated by King. Later, in 1943, Wintersteiner obtained the same alkaloid from another species of plant.

This active principle, *d*-tubocurarine chloride, is the drug most commonly used today to produce muscular relaxation or paralysis. It is important to note that it still must be biologically assayed to determine its potency. The official assay method of the United States Pharmacopeia is the rabbit head drop test. Essentially this is a test for failure of neuromuscular transmission. A series of injections of curare is given fifteen seconds apart. The end point of the assay is the inability of the rabbit to raise its head in response to a physiologic stimulus. By comparison with the activity of a standardized preparation of crystalline *d*-tubocurarine the potency of any curare sample may be measured.

The mechanism of action of this compound merits some discussion. When an impulse travels down a motor nerve, it causes depolarization of the neuromuscular junction. This wave of negativity gives rise to the so-called action potential recorded by means of various electrical measuring devices. A rapidly falling potential results within the end plate which, when it reaches a certain critical level, excites the muscle to respond with a contraction. The membrane of the end plate is rapidly repolarized in preparation for the next stimulus. Now, how does curare interfere with this process? It has been shown experimentally, chiefly by Eccles and his collaborators, that curare prevents the depolarization of the end plate, thus inhibiting development of the change in potential. If sufficient curare is given, the potential difference does not reach the critical level necessary to produce a muscle contraction. In essence, the motor impulse arrives normally at the end plate but its transmission to the muscle is blocked.

Since *d*-tubocurarine was first introduced, some compounds with similar actions have come into use. By adding two methyl groups to the very complicated structure of *d*-tubocurarine, it was possible to produce the dimethyl-*d*-tubocurarine which is sold commercially as metubine.® This compound has the same mechanism of action as curare but it is approximately ten times more potent. Whether or not it has any advantages I will leave to the clinicians to decide.

There is another agent which has been used in other countries and is now being introduced into America. This compound, which has the trade name flaxedil,® is quite different chemically from *d*-tubocurarine. It has a benzene structure, substituted with choline at three adjacent carbon atoms. In the choline nuclei ethyl groups are substituted for the usual methyl radicals. There is fairly good evidence that flaxedil, despite its chemical dissimilarity, has the same mechanism of action as *d*-tubocurarine.

There is still another group of drugs which produce the end results of curarization and which are sometimes called curarizing agents. Of course, a patient can be "curarized" only with curare; when paralysis is produced with another drug, it is incorrect to say the patient is "curarized." The terms "curare-like" cura-

riform" may be more properly applied to those agents which lead to an effect similar to that of curare.

The other agents to which I refer are the quaternary ammonium compounds which produce the same effects as curare but by a different means. The first of these compounds was developed in England by Ing, who combined two quaternary ammonium molecules separated by a straight chain of ten carbon atoms. It was named decamethonium bromide by Ing and is marketed under the trade name of syncurine.® The end result following administration of syncurine is the same as that produced by curare but the mechanisms of action of the two agents seem to be directly opposed. Syncurine prolongs depolarization at the end plate whereas curare prevents it. When the depolarization is prolonged, the end plate cannot repolarize to the normal resting state and the next nerve impulse cannot be transmitted to the muscle. Its action resembles that of acetylcholine which, if allowed to pile up at the myoneural junction, blocks the muscle response. Since syncurine acts in this manner it should theoretically be counteracted by *d*-tubocurarine. In the laboratory such is the case. The one paralyzing agent can be antagonized by the other if the experimental conditions are exactly adjusted. Actually many trials may be necessary to demonstrate the antagonism.

I do not know whether the prolonged depolarization produced by syncurine is desirable. On the whole, the mechanism of action of curare appears preferable although proof of harm from syncurine is lacking. It is known, however, that prolonged depolarization produced by other agents extended over a period of several days does lead to permanent damage.

There are a few other pharmacologic actions of these paralytic drugs which deserve mention. Curare has a histamine-like action if injected intra-arterially and, according to reports, when given intravenously. This may be manifested by a sudden drop in blood pressure, bronchiolar constriction and excessive secretion in the respiratory tract. Fortunately, such reactions have been encountered very rarely in the clinical usage of the drug. Curare and also syncurine produce a moderate degree of ganglionic blockade. I suppose there are some surgical circumstances in which this ganglionic blockade would not be desirable and use of such drugs might add another hazard to the procedure. Flaxedil does not alter ganglionic function. All these agents at least partially inhibit vagal nerve function. Flaxedil in particular is almost as effective as atropine in blocking the cardiac effects of vagal nerve stimulation so that a moderate tachycardia often follows its administration.

Finally, I would like to speak about the problems involved in the use of curare and similar drugs. The greatest danger inherent in all these compounds is, of course, respiratory embarrassment. This may occur following administration of any of them and will continue to represent a hazard until a drug is developed that will spare the diaphragm while paralyzing all other skeletal muscles. Unfortunately, there seems to be nothing specific about the end plates of the diaphragm and I doubt that any such drug will be produced. There is no real difference among these compounds in their margin of safety since the occurrence of respiratory difficulties is related to production of the desired therapeutic paralysis. Therefore, I would say without reservation that these paralytic drugs should never be used unless means are available for instituting positive pressure artificial respiration at a moment's notice.

Artificial respiration must be considered the best physiologic antidote to curare and similar drugs. I think it important to know, however, that there are also available some chemical antagonists. The one most commonly used is neostigmine, also known commercially as prostigmine.® Recently a new series of compounds related to neostigmine has been developed at the New York Hospital-Cornell Medical Center. These have not yet been marketed and have no trade names. The one most practical for clinical use is referred to by its code designation, Ro 2-2561. These chemicals depolarize the end plate of the nerve, an action opposite to that of *d*-tubocurarine, metubine and flaxedil. Since the actions are opposite, they neutralize each other. The mechanism may be most simply explained by stating that Ro 2-2561 competes with curare for the neuroeffector cell. This does not occur in the case of syncurine, which produces paralysis by depolarization. Neostigmine, Ro 2-2561, and the others of the series will not antagonize the effects of syncurine but on the contrary will increase the paralysis. I believe that the only effective source of relief for cases of respiratory difficulty following use of syncurine is artificial respiration.

DR. READER: Dr. Artusio, as an anesthetist, would you care to comment?

DR. JOSEPH F. ARTUSIO, JR.: As you all realize, the primary aim in anesthetization of individuals is the production of unconsciousness but in many surgical procedures muscular relaxation is also mandatory. Until the introduction of curare, adequate relaxation could be produced only by very deep anesthesia which was associated with disturbances of many of the physiologic mechanisms which compensated for trauma, blood loss and the like. Naturally, individuals in such a state easily went into shock when exposed even to minor stress. In present day anesthesia we can maintain very light planes of anesthesia and by the use of curare or a similar drug retain the peripheral compensating mechanisms, with adequate relaxation. This has been a tremendous boon, especially for patients considered as poor risks. Today there is hardly an abdominal operation or an endotracheal intubation performed in this institution without the aid of one of the curare preparations.

We most commonly use *d*-tubocurarine. This is an extremely effective muscular relaxant and can be employed in combination with any of the anesthetic agents. When used in association with pentothal sodium or cyclopropane, the dose of curare necessary to paralyze the individual without producing severe respiratory depression is usually between 9 and 12 mg. When used in conjunction with ether anesthesia the dose necessary to produce the same effect is in the neighborhood of 3 to 6 mg. Thus with ether only about one-third as much curare is needed as with the other anesthetics.

I must emphasize that the doses mentioned are only approximations. The paralytic effects of *d*-tubocurarine are not exactly predictable even on a dose-for-weight basis. I agree emphatically with Dr. Wescoe's statement that no one should administer curare unless he is prepared to furnish artificial respiration to the patient immediately. The antagonists to curare and flaxedil provide another means of combating the effects of overdosage, but artificial ventilation is still the treatment of choice.

Our experience with flaxedil has been limited. From Dr. Marbury's work it would appear that the usual dose in man lies between 1 and 1½ mg. per kg. This produces good muscular relaxation comparable to that produced by *d*-tubocurarine, without interfering with respiration. Flaxedil has an advantage over curare in that its effects are much more predictable. We have seen the vagal blocking action of flaxedil in patients lead to a moderate tachycardia but we have not yet decided whether this is important. Both flaxedil and curare produce their maximum effects within three minutes after intravenous injection and the effect lasts about twenty to forty-minutes.

Syncurine, the decamethonium compound, is even less predictable than *d*-tubocurarine. The dose is approximately 2 to 4 mg. in anesthetized humans and it makes little difference what anesthetic agent is used in association with it. There is not the distinction between ether and cyclopropane which must be considered when using curare.

All of these agents show cumulation if doses are repeated in less than sixty minutes. To produce the same effect as the initial dose, subsequent doses must be approximately halved.

We might add that flaxedil may eventually become the drug of choice since it does not have the ganglionic blocking action of *d*-tubocurarine. This is an advantage in that it preserves more of the peripheral compensating mechanisms to acute blood loss and trauma. Early observations, subject to confirmation, indicate that flaxedil has a second advantage over curare in that its effects are more predictable.

DR. READER: Are there any questions at this point?

DR. WALTER F. RIKER: I would like to ask Dr. Artusio, how complete is the ganglionic blockade with *d*-tubocurarine during the usual surgical procedure?

DR. ARTUSIO: That is difficult to say. I do not know any way to determine clinically the amount of ganglionic blockade. In accord with the work in the experimental laboratory, I would certainly choose a drug that did not produce a ganglionic blockade for use in those patients who may suffer trauma or acute blood loss.

DR. JOHN MCLEAN: Dr. Artusio has commented on the use of these agents in conjunction with intravenous and inhalation anesthesia. I wonder if he would say something about their use in conjunction with local anesthetics in the head region.

DR. ARTUSIO: In conjunction with local anesthesia, 3 to 6 mg. of *d*-tubocurarine will usually provide fair relaxation of the small muscles of the face with but little interference with the muscles of respiration. But again I must stress that the degree of paralysis produced by curare is not always what one would expect. Even

small doses of the drug if given to sensitive individuals may produce respiratory depression of a severe degree. I would never use it unless I was ready to offer the patient artificial respiration.

DR. MCKEEN CATTELL: In relation to the fact that the compounds of the decamethonium type cause depolarization of the end plate, I wonder whether there is a discharge from the end plate resulting in muscular fibrillation, as is the case with neostigmine.

DR. WESCOE: I do not think it is seen clinically. Does Dr. Artusio see it?

DR. ARTUSIO: It is not seen clinically.

DR. WESCOE: Experience in the laboratory indicates that with any agents that block by depolarization it is possible to find some dose at which stimulation occurs.

DR. READER: In a patient in whom the effect of curare, or one of these curare-like agents is excessive, what is the first thing to do? Do you immediately try one of the chemical antagonists or do you first start artificial respiration?

DR. ARTUSIO: There are two emergency situations that can arise after curare has been given. First, the patient may have received too much curare either because of overdosage or of unusual sensitivity to the drug. Second, the patient may have been fully curarized when the operation was for some reason suddenly terminated, thus necessitating supportive measures until the paralytic effects disappear. If there is overdosage, the prime requisite is artificial respiration. The period during which this will be needed can be shortened markedly by the chemical antagonists, but I do not think a patient should be allowed to remain in apnea while someone is running to get an anti-curare compound or is drawing the compound into a syringe. If oxygen is available, it should be given under positive pressure. Once artificial respiration under optimal conditions is established the antagonist may be given at leisure. In the second circumstance when a patient has been curarized and his respiration reduced to barely adequate levels just as the operation must be terminated, the antagonists are effective. A single injection may overcome the paralysis and render breathing adequate.

DR. JANET TRAVELL: Do you ever have to give more than one dose?

DR. ARTUSIO: Yes, if the first is inadequate. The dose of an antagonist depends upon the degree of curarization, which is best measured by the respiration. We worked out the doses required in man for one antagonist, Ro 2-2561, using the respiratory minute volume as a guide. For a completely paralyzing dose of *d*-tubocurarine 15 mg. of Ro 2-2561 were needed. When respiration was reduced to two-thirds, only 10 mg. of the antidote were needed. Five milligrams counteracted a respiratory depression of 30 to 50 per cent. For these trials the intravenous route of administration was employed.

The maximum effect of the antagonist is obtained within five minutes. If the dose is insufficient to antagonize all the curare, some paralysis will again become apparent. Then it may be necessary to give another dose of the antagonist, the dose to be calculated again on the basis of the degree of respiratory depression which remains.

DR. WESCOE: I do not think that Dr. Artusio is including neostigmine in his present discussion. The dose for neostigmine is much smaller than the other antagonists.

DR. ARTUSIO: I did not mean to include neostigmine in that dose schedule.

DR. READER: How do you tell when a patient has had too much curare? Are you immediately aware of it?

DR. ARTUSIO: Just observe the respiration, preferably by actual measurement of minute volume. The maximum effect of curare will appear within three minutes after its intravenous injection.

DR. READER: Do curare and the other drugs stimulate the central nervous system?

DR. WESCOE: Not within the dose ranges that are used clinically. All the effects are peripheral.

DR. READER: You stated that these agents affect the motor end plate of the nerve. Is there any change in the muscle cells themselves?

DR. WESCOE: The muscle remains perfectly normal. Even though paralyzed completely, so far as response to nerve stimuli is concerned, the muscle will react to direct electrical stimulation.

DR. DAVID B. THOMPSON: How are curare and other compounds handled by the body? Are there any disease states in which their use is contraindicated?

DR. READER: Dr. Riker, would you like to answer the first part of the question?

DR. RIKER: There is no information on the metabolism of *d*-tubocurarine by the animal organism. We do not know what happens to it after it leaves the myoneural junction. There is some not entirely conclusive evidence that it

may be eliminated in the urine. Further study of these aspects of the subject is badly needed.

DR. READER: Are there any chemical tests for curare?

DR. RIKER: No, their unavailability is at present a real handicap.

DR. THOMPSON: What are the contraindications to the curarizing drugs?

DR. READER: Dr. Artusio, do you have an opinion about that?

DR. ARTUSIO: The only disease which would make me use curare with caution is myasthenia gravis. There certainly is a possibility that administration of the drug to an unrecognized myasthenic might result in paralysis more profound than was anticipated. I cannot think of any other disease that might cause difficulty.

INTERN: How would you handle an obvious case of myasthenia being maintained on prostigmine, which is an antagonist to curare?

DR. RIKER: Just discontinue the prostigmine. These patients may come to you practically paralyzed.

DR. WESCOE: I would not even say that myasthenia is a contraindication to the use of curare. In my opinion that belief, while traditional, has little to support it. Curare can be given to a myasthenic but must be administered judiciously. Even if difficulty arises, nothing serious is going to happen so long as artificial respiration is maintained.

DR. READER: Would the antagonist of choice for a myasthenic be neostigmine?

DR. WESCOE: No. The antagonist of choice for the curare agents is one of the shorter acting compounds. Neostigmine in too large doses is very likely to cause trouble because it possesses a curariform action like that of syncurine. It is difficult to predict whether the stimulating or depressant effects will predominate. It is quite possible to augment the paralysis of curare by adding to it the paralytic effects of too much prostigmine. This cannot happen with the briefer acting newer antagonists.

DR. READER: Dr. Dunning, how do you feel about the question of contraindications? Are there any neurologic conditions which might increase the dangers of these paralytic drugs?

DR. HENRY S. DUNNING: I should think a patient who has had poliomyelitis with some residual weakness of his respiratory muscles would run greater risks of respiratory difficulties than would a normal individual.

DR. READER: How about amyotrophic lateral sclerosis?

DR. DUNNING: I would include that in the same category. We often see cases of amyotrophic lateral sclerosis, poliomyelitis and even neuritis in which the intercostal muscles are not working. This is often missed in an ordinary physical examination. I should think such a condition might increase the dangers. Surely the patient's respiratory apparatus should be very carefully examined before curare is given.

DR. READER: I was interested in your remark about poliomyelitis because there was once much agitation for the use of curare in acute poliomyelitis. Dr. Plum, could you give us a brief description of the use of curare in poliomyelitis? What was the rationale of this treatment and why was it abandoned?

DR. FRED PLUM: I never used it so I can only report the experience of others. My understanding is that curare was used in an attempt to break up joint limitation which otherwise occurred in individuals with painful and stiff muscles. In other words, the normal motion about a joint was limited because of pain and stiffness in adjacent muscles. By curarizing those muscles it was hoped to achieve earlier mobility and therefore earlier physical reeducation. I believe the reason this therapy was given up was simply that long term studies showed that the patients who were curarized did not get well any faster. Indeed, histologic studies on muscles from those patients showed a good deal of actual rupture of the muscle fibers about the joints. Some observers believed that groups of paralyzed muscles were being overstretched and damaged. I have some difficulty visualizing how this could happen if they maintained muscles within the usual states of stress. Nevertheless, even though the curare was not detrimental, it accomplished no demonstrable benefit.

DR. READER: Curare was also popular at one time for patients with arthritis, based on the same reasoning Dr. Plum has described. Dr. Wescoe, was there any value in this therapy?

DR. WESCOE: I do not know what the status of therapy is there. Dr. Travell might have something to add.

DR. TRAVELL: There are very few people who use it. To do any good in a chronic disease like arthritis curare would have to be given on a long term, ambulatory basis. It is not possible to do

this safely. There are treatments more effective and more easily used.

DR. CATTELL: Are we trying to keep the chemical characteristics of these antagonists under a wrapper? It might be interesting to hear about their relationship to acetylcholine and the other members of that group.

DR. WESCOE: These compounds were originally developed because it was noted that neostigmine had several actions, one of which was a potent anti-cholinesterase action. Previously it had been shown by Stedman that much of the anti-cholinesterase action of neostigmine is due to the dimethylcarbamate grouping on its basic trimethylphenylammonium structure. We first requested the chemist to replace the carbamic acid end of the molecule with an acetyl radical, to give a compound closely related structurally to acetylcholine. Other compounds studied included one with a hydroxyl substitution of the carbamate grouping and also the basic trimethylphenylammonium salt. The anti-curare action of the three modifications of the neostigmine molecule are essentially similar.

INTERN: Originally you stated that the anti-curare compounds cause depolarization of the end plate of the nerve. That is also the way in which you said that syncurine paralyzes. Why then don't these antagonists block neuromuscular transmission?

DR. WESCOE: In the laboratory they do. Small doses of the antagonists cause only stimulation with marked muscle fasciculations. If larger doses are given, this brief period of stimulation is followed with a curare-like paralysis. But this paralysis is of brief duration, measured in minutes, and most importantly it has been impossible in the laboratory to show any summation between the paralytic actions of curare and the antagonists. If a patient manifests effects of curare, the antagonists do not add to the paralysis but instead counteract it. Within six minutes the actions of the antagonists are over and, if curare effects have returned, an additional dose can be given without any fear of adding to the paralysis.

DR. CATTELL: Is the antagonist entirely eliminated in a matter of minutes?

DR. WESCOE: That is a difficult question. The effects certainly disappear rapidly but we do not know the fate of the compound itself. We do not know how it is eliminated.

DR. READER: Some time ago I heard much discussion of a long-lasting curare-like compound. Wasn't some new drug developed to provide a prolonged effect?

DR. WESCOE: That was probably mephenesin which can be given over relatively long periods to promote muscular relaxation. However, the paralysis is mediated by an action on the reflex center of the brain and spinal cord and thus does not resemble curare in its mechanism of action. No drug with a true curariform action and a prolonged period of action has been developed. The Romansky formula developed for repository penicillin has been used to provide slowly absorbed deposits of *d*-tubo-curarine. I do not know of anyone still using it.

DR. READER: Wasn't that quite dangerous?

DR. WESCOE: The unpredictability of absorption of curare was added to the unpredictable paralytic effects of the drug.

DR. TRAVELL: The total amount given in slowly absorbed preparations would have to be much greater than the usual single therapeutic dose. That might be a real hazard!

DR. WESCOE: I think that is true.

DR. LEON J. WARSHAW: I wonder whether anyone has used curariform drugs by intra-arterial injection when relaxation of the muscles of a limb is desired for the reduction of fracture.

DR. READER: Does anyone know about that? Dr. Wescoe or Dr. Artusio, have you ever heard of its use in such circumstances?

DR. ARTUSIO: No.

DR. WESCOE: The only intra-arterial studies are experimental.

DR. WARSHAW: Is it possible that by giving a small dose into an artery and blocking the venous return from the area, a local effect might be obtained without any systemic or respiratory changes?

DR. READER: That certainly sounds like a practical idea. Are there any other questions?

DR. RIKER: I would like to ask Dr. Artusio if he has noted any histamine-like or ganglionic blocking actions of *d*-tubocurarine during surgical procedures.

DR. ARTUSIO: We usually give curare intravenously and by this route its histaminic actions rarely occur. It is difficult to determine by clinical means the presence of ganglionic blockade. We have not been impressed by its occurrence during operations. Since, however, we know that it may happen, I think it is a factor to be considered before administering curare to patients who may suffer much trauma or blood loss during operation.

DR. CATTELL: I would like to ask whether Dr. Artusio always intubates the patient before using these drugs.

DR. ARTUSIO: We never give curare without prior intubation so that we have a ready pathway for artificial ventilation. That is the safest method to employ and the safest rule to make in a large service such as we have here.

DR. CATTELL: Would you say curare should never be used without intubating first?

DR. ARTUSIO: It should not be used unless the proper apparatus is at hand and the individual who is administering the curare can produce unobstructed artificial ventilation.

DR. READER: That brings up another point, however. Do you ever use curare in order to intubate someone?

DR. ARTUSIO: Oh yes, we do that very often but of course the intubation is accomplished immediately and that is the purpose in giving the curare, to produce an airway. I have not seen any individual who had had curare whom it was not possible to intubate.

DR. READER: In a patient with laryngeal spasm, or some other condition for which tracheotomy has heretofore been indicated, is curare plus intubation better than tracheotomy?

DR. ARTUSIO: I believe that an individual in severe laryngospasm should first be treated with positive pressure oxygen by means of a mask and bag in an attempt to break the spasm. Anesthetists usually have atropine available in their equipment. A large dose of atropine, 0.8 to 1 mg. intravenously, may be of great help in abolishing the laryngospasm. If curare is immediately available, and I mean immediately because laryngospasm cannot go on long without producing central nervous system damage, it may be used. However, if I could not break the laryngospasm with positive pressure oxygen, I would have the surgeon begin tracheotomy while intubation was being attempted.

DR. READER: Do you use curare with spinal anesthesia?

DR. ARTUSIO: It may have some value in spinal anesthesia if the muscular paralysis has worn off while the sensory paralysis is still intact. A small dose may give satisfactory relaxation for a while longer. We have not used curare in that fashion. If in spinal anesthesia the relaxation is poor, we convert to a general inhalation anesthesia.

DR. READER: Dr. Victor Marshall told me that he finds curare essential in doing prostatectomies by the transurethral route because it combats priapism. Were those patients receiving spinal anesthesia?

DR. ARTUSIO: Some of them were under spinal anesthesia. We used small doses of curare, 3 to 6 mg., in the conscious patient, which diminished the priapism. We were, of course, always ready to intubate the patient.

DR. READER: Dr. Wescoe, do you have a comment?

DR. WESCOE: I question giving curare with a local anesthetic because it is my impression that the surgeon does not always take the patient seriously when he says the sensory anesthesia is diminishing. It would be an unpleasant experience not to be able to respond to a painful stimulus.

DR. ARTUSIO: We have given curare to a few conscious individuals with severe muscle spasm. They had low back muscle spasms which elicited terrific reflex pains whenever they moved. We gave them 3 to 6 mg. of *d*-tubocurarine intravenously, got them out of bed and walked them around. Much to my surprise the spasm was completely abolished and did not return.

DR. READER: Were they able to walk unassisted?

DR. ARTUSIO: Yes. You must remember that the condition of the patient partially determines the response to curare. Earlier I mentioned the fact that ether sensitizes the myoneural junction to curare so that the full curarizing dose in an etherized patient would be about one-third the dose for a patient during cyclopropane anesthesia. Without any anesthesia the dose would be slightly higher. In a conscious, unanesthetized human, 3 to 6 mg. of curare will produce no respiratory difficulties and only slight muscular weakness.

SUMMARY

DR. READER: Dr. Wescoe has discussed the pharmacology of *d*-tubocurarine and flaxedil which are believed to produce muscle relaxation by preventing depolarization of the nerve end plate. Syncurine, on the other hand, leads to the same result by prolonging depolarization. This distinction is important in the use of the anticurare agents since the latter do not counteract the effects of syncurine. There is general agreement that artificial respiration is the best treatment for respiratory difficulties arising after administration of any of these neuromuscular blocking agents. Indeed, these drugs should not

ever be given unless facilities for proper ventilation are immediately available. However, with the exception of syncurine, the chemical antagonists may be useful in that they can immediately, completely and safely antagonize the effects of curare. It seems to be the opinion that flaxedil may prove superior to *d*-tubocurarine in that it does not alter ganglionic transmission and its effects are more uniform than those of curare. The point has been made that curare and the other drugs are quite unpredictable in their actions. However, if this characteristic is taken into account, and if the means are available to produce artificial respiration, there are few contraindications to the use of these drugs.

Clinico-pathologic Conference

Miliary Pulmonary Infiltration with Hydrothorax and Ascites

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Department of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. H. (No. 188544), a sixty-five year old white married housewife, entered the Barnes Hospital on August 31, 1950, complaining of shortness of breath, swelling of the abdomen and fatigue. Because of the patient's condition the history was obtained with difficulty and was not considered adequate.

The family history was of interest in that one brother died of "lung disease" of unknown etiology. As far as could be determined the patient herself had enjoyed generally good health. There was no known previous serious illness; and although her appetite had been poor for years and her diet had been lacking in protein, an occasional non-productive cough had been her only known symptom. She had kept a dog in her home for many years.

One year before admission the patient developed uterine prolapse and a complicating urinary infection; she was admitted to a local hospital where a hysterectomy was performed. The general physical examination was said to have been negative at that time. Following the operation, however, the patient failed to regain full strength and she noted the onset of dyspnea on exertion. Six months prior to entry she developed a "severe cold" associated with a productive cough. These symptoms persisted and after three weeks the patient sought medical attention. Her physician told her that she had a high fever and made a diagnosis of virus pneumonia. She was treated with penicillin and a sulfonamide with some transient improvement, but she then developed increasing fatigue, dyspnea, anorexia and cough, and she lost weight.

Three months before admission to the Barnes Hospital, she was readmitted to the local hospital where she remained for ten days. At that time her temperature was 97.4°F. and physical examination revealed pallor, malnutrition, signs of pleural fluid in the left lower chest, ascites, an enlarged, firm, non-tender liver and ankle edema. The laboratory findings included normal white cell and differential counts. The non-protein nitrogen was 37 mg. per cent and the cephalin-cholesterol flocculation test 4 plus. An electrocardiogram was said to have been "abnormal" and a chest film revealed cardiac enlargement and a left pleural effusion. A gastrointestinal x-ray series was negative, but cholecystograms revealed non-function of the gallbladder.

A thoracentesis was performed; smears of the fluid showed many intracellular organisms which were thought to be histoplasma capsulatum. In addition, there were cigar-shaped forms, thread-like structures resembling mycelia, and some acid-fast organisms which were "not characteristic" of tubercle bacilli. Cultures of the pleural fluid on Sabaraud's medium and on blood agar were negative. During her hospital stay the patient's temperature ranged between 99° and 100°F.

After discharge she experienced progressive swelling of the abdomen and legs and was once again admitted to the local hospital. Physical examination revealed that she was moderately dyspneic. Signs of fluid were present over both lung bases and the heart was moderately enlarged. The abdomen was distended with fluid and there was pitting edema of the legs. A chest film showed cardiac enlargement and bilateral pleural effusions, with the most marked effusion on the left. Thoracentesis and abdominal paracentesis were performed, but examination of the fluids failed to show the organisms previously described.

During her first hospital week the patient's

temperature ranged between 101° and 101.5°F. but subsequently it became almost normal. She was given small doses of digitalis and a transfusion and was discharged. After leaving the hospital she once again had increasing abdominal swelling and edema of the legs, and she was referred to the Barnes Hospital.

At the time of entry physical examination revealed the temperature to be 36.8°C., pulse 90, respirations 20 and blood pressure 155/90. The patient was thin, weak and appeared chronically ill. Her complexion was sallow. Examination of the skin revealed it to be of poor turgor, and there were several decubitus ulcers over her back. The retinae showed moderate arteriosclerotic changes but no hemorrhages or exudates. Examination of the upper respiratory tract was negative except that the tongue was extremely red. Examination of the chest revealed flatness, absent fremitus, and diminished breath sounds over the entire right chest. The heart presented no abnormalities. The abdomen was moderately distended with fluid, but the liver could be felt 4 cm. below the right costal margin. The feet and legs were markedly edematous.

The laboratory data were as follows: Blood count: red cells, 4,910,000: hemoglobin, 16.3 gm; white cells, 9,100; differential count: stab forms, 13 per cent, segmented forms, 78 per cent; lymphocytes, 3 per cent; monocytes, 6 per cent. Urinalysis: specific gravity, 1.019; albumin, trace; sugar, negative; bilirubin, 1.2 mg; per cent; urobilinogen, 0.49 mg. per cent; centrifuged sediment: many clumped white blood cells and many bacteria. Urine culture: B. aerogenes. Stool examination: guaiac negative. Blood Kahn test: negative. Blood chemistry: Non-protein nitrogen, 18 mg. per cent; sugar, 79 mg. per cent; chlorides, 96 mEq./L.; total proteins, 6.9 mg. per cent; albumin, 2.6 gm. per cent; globulin, 4.3 gm. per cent; alkaline phosphatase, 4 Bodansky units; cephalin-cholesterol flocculation test, 3 plus; thymol turbidity, 9.1 units; total cholesterol, 91 mg. per cent; cholesterol esters, 50 mg. per cent; BSP retention: 60 per cent in thirty minutes; sodium bilirubinate, 0.44 mg. per cent; bilirubinglobin, 1.64 mg. per cent. Venous pressure: 85 mm of water. Circulation time (decholin): fifteen seconds. Roentgenogram of the chest: there was distinct cardiac enlargement, chiefly of the left ventricle; a pleural effusion was present at the right base and there was pulmonary congestion. In addition a fine mottling was seen throughout both lung fields. Electrocardiogram: slightly depressed S-T segments in leads II, III and AVF; inverted T waves in V_4, V_5 and V_6; flat T waves in leads I, II, III and AVF.

On the day following admission a right thoracentesis was performed and 1,600 cc. of pleural fluid were removed. The fluid had a specific gravity of 1.015. Sections made from a cell block revealed no malignant cells and gave no clue to etiology. An abdominal paracentesis was done and 700 cc. of cloudy yellow fluid was removed. This fluid had a specific gravity of 1.011 with a total protein of 0.88 gm. per cent. The cell count was 500 of which 50 per cent were segmented and 50 per cent mononuclear forms. No organisms were seen. Cell block section of the ascitic fluid revealed mycelia and spores, but these were considered to be contaminants. Sternal bone marrow aspiration was carried out. Smears of the marrow were negative for organisms, but on culture Histoplasma capsulatum was recovered two days before the patient's death. Many examinations of pleural fluid obtained by repeated thoracenteses were made but neither organisms nor tumor cells were seen. Histoplasmin and first strength PPD skin tests were negative, and the histoplasma complement fixation test was negative. Microscopic sections of cell blocks made from pleural fluid, in which organisms were originally described, were reviewed by a mycologist who suggested the possibility of sporotrichium infection. Because of the possibility of sporotrichosis potassium idodide was given in increasing doses without favorable effect. The patient became weaker and continued to be anoretic and lethargic. Edema of the legs became more marked, and the patient was given intravenous salt-free albumin. Because of poor food intake she was maintained by intravenous alimentation and vitamin supplements. Despite the latter substances, however, she developed acute glossitis and stomatitis. At the end of her second hospital week the following laboratory data were obtained: prothrombin time, 70 per cent of normal; total proteins, 7.0 gm. per cent; albumin, 2.4 gm. per cent; globulin, 4.6 gm. per cent; non-protein nitrogen, 12 mg. per cent; chlorides, 88 mEq./L. Red blood cell count, normal; hemoglobin, normal; white blood cell count, 13,350; differential, normal. Subsequent roentgenograms of

the chest again revealed bilateral miliary mottling in addition to the pleural effusions.

Three weeks after admission another paracentesis was performed. The fluid had the characteristics of a transudate and no organisms were seen on smear. The non-protein nitrogen rose to 32 mg. per cent and then to 61 mg. per cent. The patient had increasing dyspnea, she vomited frequently and adequate nutrition could not be maintained. Weakness, lethargy, anorexia, hypotension and dehydration were prominent. The cephalin-cholesterol flocculation test was 4 plus, and the thymol turbidity 5.3 units. Repeated electrocardiograms showed no evidence of hyperkalemia although the T waves were upright. During her hospital stay the patient exhibited a swinging type of low grade fever, but in the last few days it rose to between 38° and 39°C. She died on September 28, 1950, shortly after developing signs of bronchopneumonia.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presents a most interesting problem in differential diagnosis. During the period that this patient was in another hospital in this community a diagnosis of histoplasmosis was made. Subsequently when she was admitted here, bone marrow examination was performed; and although examination of smears of the marrow failed to reveal Histoplasma capsulatum, culture of the marrow was reported positive for these organisms two days before the patient died. Dr. Elliott, would you begin the discussion by commenting on the chest films, particularly the presence of miliary mottling in the lung fields? What is the significance of this particular finding?

DR. GLADDEN V. ELLIOTT: The miliary infiltrate which was noted in this patient's chest roentgenogram was compatible with several etiologic factors. Such lesions are sometimes due to pulmonary congestion occurring in acute heart failure, and they may occur on the basis of hemosiderosis following long-standing heart failure. Excluding these two explanations one must certainly consider either histoplasmosis or miliary tuberculosis.

DR. ALEXANDER: In an attempt to substantiate the diagnosis of histoplasmosis, skin tests were performed and serum was collected for a complement fixation test. As was noted in the protocol the skin test was negative, and the complement fixation test, which was done by Dr. Furcolow of the United States Public Health Service, was also negative. Dr. Wells has been particularly interested in this disease, and I have asked him to review the significance of these particular data.

DR. JOHN G. WELLS: The significance of the histoplasmin skin test and of the complement fixation test in substantiating the diagnosis of histoplasmosis has been discussed rather widely in the recent literature. It can be said at the outset that no definitive conclusions have as yet been reached. Several important observations have been made by Furcolow.[1] He noted that apparently healthy patients who had positive histoplasmin skin tests frequently lost their skin reactivity to histoplasmin during the course of various acute illnesses other than histoplasmosis. After recovery the patients again exhibited positive histoplasmin tests. The incidence of positive histoplasmin skin tests also decreased with increasing age. The experience at the Children's Hospital here is consistent with the foregoing results. Thus Dr. Klingberg[2] has recently summarized ten cases of histoplasmosis in which the diagnosis was proven in all by culture and in nine by subsequent pathologic examination. None of the nine patients who died, all of whom had repeated positive cultures, had a positive skin test or a positive complement fixation test. In the one child who recovered the skin and complement fixation tests were negative during the acute stage of the disease, but both became positive after the child recovered. In one of the recent Barnes Hospital cases in which the diagnosis of histoplasmosis was proven at autopsy, the skin test was negative. It seems clear, therefore, that negative skin tests and/or negative complement fixation tests in acutely ill patients do not rule out the diagnosis of histoplasmosis.

DR. ALEXANDER: Thank you for your summary, Dr. Wells. The information you have presented is pertinent in the case under discussion today. The fact that both the skin and complement fixation tests were negative in this gravely ill woman cannot be considered to militate against the diagnosis of histoplasmosis. Also of interest in this particular case was the presence of both pleural effusions and ascites. In the collected literature on the subject up to 1945, and

[1] FURCOLOW, M. L., EMGE, M. E. and BUNNELL, I. L. Depression of tuberculin and histoplasmin sensitivity associated with critical illness. *Pub. Health Rep.*, 63: 1290, 1948.

[2] KLINGBERG, W. G. Generalized histoplasmosis in infants and children. *J. Pediat.*, 36: 728, 1950.

indeed even later than that, not a single case of histoplasmosis with which ascites was associated was reported. Pleural effusion is also quite uncommon. The latter fact seems to me to be particularly unusual because the organism frequently attacks the lungs and the subpleural tissues; one would expect, therefore, that pleural effusion would be encountered in a significant per cent of cases. Dr. Wells, what have you found out about this particular point?

DR. WELLS: Pleural effusion was not observed in any of the ten cases at the Children's Hospital. One of the recent patients with histoplasmosis in this hospital had both a pleural effusion and ascites; but the concomitant association of severe hypoproteinemia and of congestive heart failure made it difficult to determine the role of the infection *per se* in the development of fluid in the two body cavities. In two other recent cases of proven histoplasmosis in children, one patient had a definite pleural effusion demonstrated by x-ray, and in the other an interlobar effusion was suspected.[3] Nonetheless as you have pointed out, Dr. Alexander, the accumulated clinical evidence indicates that ascites and pleural effusion are rare in histoplasmosis.

DR. ALEXANDER: You have had much experience with this disease, Dr. Goldman. Have you found pleural effusion in any of the patients you have followed?

DR. ALFRED GOLDMAN: No, I have not.

DR. ALEXANDER: Dr. Flance, would you comment on this point?

DR. I. JEROME FLANCE: I agree entirely with what has been said.

DR. ALEXANDER: It can be assumed then that if this patient indeed had histoplasmosis, she was one of the very few in whom ascites and pleural effusion have been encountered. Because of this fact the possibility that this patient's major disease was something other than histoplasmosis must be considered. Does anyone wish to suggest an alternative diagnosis?

DR. W. BARRY WOOD, JR.: Since Dr. Elliott believed that the miliary mottling in the chest film was compatible with tuberculosis, that diagnosis must certainly be considered. Further, at one point during her stay at the other hospital acid-fast organisms were present in the pleural fluid.

[3] WHEELER, W. E., FRIEDMAN, J. and SASLAW, S. Simultaneous non-fatal systemic histoplasmosis in two cousins. *Am. J. Dis. Child.*, 79: 806, 1950.

DR. ALEXANDER: I would agree that tuberculosis certainly is a distinct possibility although the fact that the pleural and ascitic fluids both had characteristics typical of transudates is disturbing. Dr. Massie, this patient had an enlarged heart and an abnormal electrocardiogram. What importance do you ascribe to cardiac failure *per se?*

DR. EDWARD MASSIE: When she was admitted to the Barnes Hospital the patient's venous pressure and circulation time were both normal. Although she may have had mild failure, I doubt that it played a major role in the general process.

DR. ALEXANDER: Are there other suggestions?

DR. ROBERT J. GLASER: One other diagnosis which should be mentioned is that of collagen disease. The bizarre clinical picture which she presented can be explained on that basis.

DR. GOLDMAN: It is possible that this patient had a fungus infection plus another disease process such as carcinomatosis or tuberculosis. I believe the chest findings were compatible with miliary carcinomatosis as well as with tuberculosis or histoplasmosis. I also agree with Dr. Glaser that collagen disease must be considered.

DR. ALEXANDER: If this patient had had disseminated carcinomatosis, wouldn't you have expected one of numerous cell blocks which were made to have shown malignant cells?

DR. GOLDMAN: I doubt that examinations of cell blocks made from pleural and ascitic fluids of patients with carcinomatosis are positive in more than 50 per cent of cases.

DR. ALEXANDER: Isn't the diagnosis more difficult in the case of ascitic fluid than pleural fluid?

DR. GOLDMAN: There are more false positives with ascitic fluid than with pleural fluid.

DR. ALEXANDER: Dr. Wood, you have suggested that this patient had miliary tuberculosis. In my examination of the record I discovered that fifteen tuberculin skin tests were done and all were negative. Does that finding disturb you?

DR. WOOD: It does to some extent but not completely. The situation in the terminal phase of tuberculosis may be similar to that to which Dr. Wells has alluded in histoplasmosis; that is, PPD skin tests may become negative. Such a sequence of events does not always occur in tuberculosis.

DR. ALEXANDER: Dr. Goldman, should disseminated sporotrichosis be considered in the absence of skin lesions?

DR. GOLDMAN: Usually sporotrichosis, of course, does involve the skin, but it may also produce pulmonary lesions.

DR. ALEXANDER: Does disseminated sporotrichosis occur in this country without skin lesions, Dr. Moore?

DR. MORRIS MOORE: I know of only one such case.

DR. GLASER: Dr. Alexander, when you prepared this protocol you must have been impressed with the fact that the patient kept a dog in her house because you specifically mentioned it. Would you tell us the significance of that information?

DR. ALEXANDER: When I first noted the statement about the dog in the history, I was not impressed with it. Subsequently, Dr. Rosecan pointed out to me that dogs may be infected with histoplasma, and he suggested that the statement should be included.

DR. WELLS: It is of interest in that regard, Dr. Alexander, that very exhaustive studies have demonstrated Histoplasma capsulatum in dogs, cats, Norwegian rats, house mice, skunks and chipmunks.[4] It is thus widely distributed among animal life.

DR. ALEXANDER: Dr. Kenamore, when this patient was first referred to you, what was your opinion about the etiology of her disease?

DR. BRUCE D. KENAMORE: We were quite puzzled by the clinical picture and laboratory data which did not seem to us consistent with a diagnosis of tuberculosis; we of course considered histoplasmosis seriously, and we asked Dr. Moore's help in delineating the problem.

DR. ALEXANDER: Would you comment, Dr. Moore, on your interpretation of the various cultures and smears?

DR. M. MOORE: Although acid-fast organisms were said to have been found in smears of the fluid obtained at the time of the first thoracentesis, I was never able to demonstrate any. I did find some intracellular organisms which suggested Histoplasma capsulatum but they were very few in number and, in the absence of a positive culture at that time, I expressed doubt as to that diagnosis. In regard to the cigar-shaped cells which were described, the possibility of sporotrichosis came to mind because in tissue this fungus may produce cigar-shaped cells. Against the diagnosis of sporotrichosis, however, was the fact that these cigar-shaped bodies stained very well. Further, the presence of very large cells is quite uncommon in sporotrichosis. I was thus unable to make a definitive diagnosis, but on the basis that sporotrichosis was a possibility, albeit an unlikely one, I suggested that iodides be given. Iodide therapy was without effect.

DR. ALEXANDER: Iodide is specific for sporotrichosis, is it not?

DR. M. MOORE: Yes, it is the one fungus infection for which iodide is specific.

DR. WELLS: We asked Dr. Henry Pinkerton of the Department of Pathology of St. Louis University Medical School to examine the slides which Dr. Moore has described to see if he thought toxoplasmosis merited consideration. Dr. Pinkerton did not believe that the cellular forms were compatible with that diagnosis.

DR. ALEXANDER: Dr. Moore, you saw the culture of the bone marrow which was reported to be positive for histoplasma two days before the patient died. Did you confirm the report?

DR. M. MOORE: Yes, the culture was unequivocally positive for histoplasma capsulatum.

DR. ALEXANDER: On the basis of that finding, one certainly would assume that the patient had histoplasmosis.

DR. M. MOORE: There can be no question that the bone marrow culture was positive for the organisms; whether or not the patient had histoplasmosis, however, may be another problem.

DR. ALEXANDER: Do patients carry these organisms?

DR. M. MOORE: I do not know.

DR. CARL V. MOORE: In every instance of which I am aware, when histoplasma was cultured from the bone marrow, the patient was shown to have disseminated histoplasmosis.

DR. WOOD: I believe I saw this patient in consultation with Dr. Kenamore. If I remember correctly, I thought the evidence favored histoplasmosis as the most likely diagnosis. I must admit that at that time I was unaware of the infrequency with which pleural effusion and ascites associated with histoplasmosis. Had I had that information, I might not have been as willing to make the diagnosis. After the positive culture was recovered, we felt certain that the patient had histoplasmosis.

DR. ALEXANDER: I believe that the evidence distinctly favors the diagnosis of histoplasmosis. Other possibilities include tuberculosis and sporotrichosis, but these are less likely. I doubt

[4] EMMONS, C. W. Animal reservoirs and other sources of pathogenic fungus, Histoplasma capsulatum. *Am. J. Pub. Health*, 40: 436, 1950.

that any of us would be surprised if this patient were found to have more than a single disease entity responsible for the entire clinical picture.

Clinical Diagnosis: Histoplasmosis.

PATHOLOGIC DISCUSSION

DR. MENARD C. IHNEN: At autopsy the patient was well nourished in spite of her long illness. The pertinent external findings were scattered petechiae on the flexor surfaces of the arms and anterior surfaces of the legs and slight edema of the legs. In the thorax there were 500 cc. of bloody pleural fluid on the right and 100 cc. of clear fluid on the left. There were rather dense fibrous adhesions over the middle and lower lobes of the right lung. On the surfaces of both lungs, but more clearly seen on the left, there were increased lymphatic markings accompanied by tiny, grey, firm nodules 1 or 2 mm. in diameter. Several slightly enlarged lymph nodes at the hilum of the right lung contained calcium and white granular material. Throughout the parenchyma of the lungs, particularly in the lower lobe of the right lung, there were fairly well circumscribed 2 mm. grey nodules. In the lower lobe of the left lung there was a lesion 3 cm. in diameter that was grey-red, indistinctly outlined and slightly granular. The pericardium was severely thickened, particularly over the right lateral surface. The tissue had a granular, firm, grey-yellow appearance; it was moist and did not dissect like fibrous tissue. The heart was not enlarged and it showed no other pertinent lesion.

In the abdominal cavity there were 600 cc. of clear fluid. The mesenteric lymph nodes were not unusual nor was the peritoneum. The liver weighed 1,000 gm. and the surface was finely nodular. These nodules were grey-yellow and slightly raised; the average was no larger than 4 mm. The organ did not cut with increased resistance, and nodules similar to those on the capsular surface were present throughout all parts. The spleen was of normal size and consistency; on the cut surface, in addition to many lymphoid follicles, scattered grey soft areas that were of a slightly irregular outline and a little larger than lymphoid follicles were apparent. The surfaces of the kidneys were very finely granular. Tiny grey nodules similar to but smaller than those in the liver were scattered over the surfaces and throughout the medulla and cortex. There were linear grey foci in the pyramids. The gastrointestinal tract was of grossly normal appearance, as were the pancreas, adrenals, bone marrow and gallbladder.

DR. GUSTAVE J. DAMMIN: The usual gross features in histoplasmosis are a striking involvement of the lymph nodes with only occasional lesions of macroscopic proportions in the viscera. The clinical diagnosis of histoplasmosis seemed acceptable in this case, however, as parenchymal lesions are known to occur with a resulting picture of a disseminated granulomatous process similar to some other fungal diseases and tuberculosis. A particularly illustrative case has been described by Dublin, Culbertson, and Friedman.[5] With the clinical diagnosis of histoplasmosis confirmed by culture and knowledge of the possibility that gross lesions of that type might occur, very little else was considered in this case until the microscopic sections were studied.

In Figure 1 one of the small nodules described in the lungs is illustrated. The lesion is a typical tuberculoid focus with some necrosis in the center and a granulomatous reaction with two giant cells at the periphery. The large lesion in the lower lobe of the left lung had the microscopic appearance illustrated in Figure 2. There is total filling of the alveoli with cells and an exudate that has undergone caseous necrosis with consequent obliteration of the outlines of the alveolar walls. A section of the greatly thickened pericardium (Fig. 3) shows giant cells and the same type of granulomatous reaction with some fibrosis. An identical granulomatous thickening involved the visceral and parietal layers of both the pericardium and right pleura. The lymph nodes contained a great deal of necrosis toward their centers but a distinct granulomatous reaction at the periphery. Similar lesions were present in the spleen, and Figures 4 and 5 show the miliary granulomas in the liver and bone marrow. The cellular elements in the uninvolved areas of bone marrow are not remarkable. The particular granuloma illustrated happens to have more necrosis than some; others had more fibrous reaction. The nodules presented a continuous series representing various stages between necrosis and fibrosis. With the usual stains they were compatible with and were first accepted as lesions of histoplasmosis. In sections of the adrenal (Fig. 6), although no lesions were observed grossly, there are a few foci which have the appearance of those noted in the organs already described. The lesions

[5] DUBLIN, W. B., CULBERTSON, C. G. and FRIEDMAN, H. P. Histoplasmosis. *Am. Rev. Tuberc.*, 58: 562, 1948.

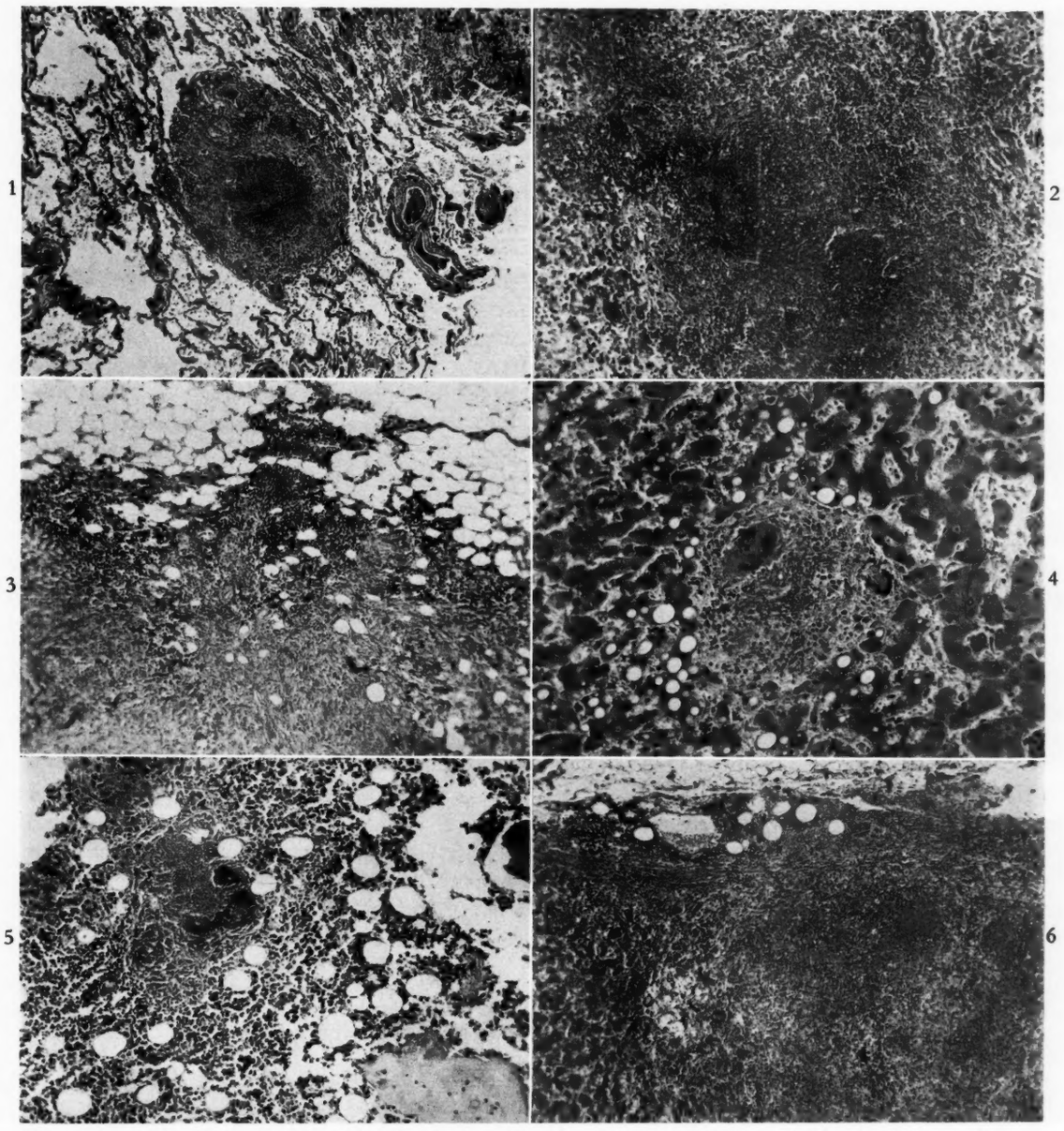

FIG. 1. A nodule of miliary tuberculosis in the lung; in this and all other lesions acid-fast bacilli were demonstrated; no fungi were seen despite the positive culture of Histoplasma capsulatum during the patient's life.
FIG. 2. A focus of tuberculous pneumonia in the lower lobe of the left lung.
FIG. 3. Tuberculous pericarditis; the pleura of the right side had a similar microscopic appearance.
FIG. 4. Miliary tubercle in the liver.
FIG. 5. Miliary tubercle with central necrosis in the bone marrow; the remaining marrow around this and similar lesions was not remarkable.
FIG. 6. Tuberculosis lesion in the adrenal.

recognized grossly in the kidney as pyelonephritis proved to be of a granulomatous nature similar to the miliary nodules.

No organisms resembling Histoplasma capsulatum were found in any of the routine hematoxylin and eosin sections. This was contrary to our experience in other cases of disease due to this cause, but to make the recognition of any such fungi easier most of these sections were also stained by the periodic acid-Schiff reaction of McManus. This stain is particularly useful because of a substance in the capsule of the fungi that is presumably of a polysaccharide nature and stains specifically. We might also

mention that although there is an acid-fast component in histoplasma, it is not of such amounts that the acid-fast stain regularly demonstrates the fungi; about a third of the organisms will stain with the usual acid-fast stain. We have not been successful in demonstrating any fungi in these sections by any method, but with the Ziehl-Nielsen stain acid-fast bacilli are present in all the lesions described. The report of acid-fast bacilli in pleural fluid removed four months before the patient's death is, therefore, more consistent with the lesions found at autopsy than the various preparations interpreted as histoplasma.

The original slide on which a diagnosis of histoplasmosis was made contained organisms with the morphologic characteristics of that fungus, but a negative culture at that time was very disturbing as cultures are more often positive than is the histologic recognition of the organism. The same problem is well reflected in a startling report by Dr. Alan Raftery[6] that in 436 appendices which were examined microscopically over 10 per cent contained organisms morphologically resembling Histoplasma capsulatum. That paper was discussed by Drs. R. J. Parsons, H. Reimann and others and the consensus appeared to be that positive identification of the specific organism is difficult even with cultures and treacherous when based on morphologic criteria alone. In the present case on two occasions, once with pleural fluid and once with ascitic fluid, organisms were described as having the morphologic characteristics of histoplasma, yet cultures made on the same material were negative. Cultures of blood, brain and lung at autopsy did not demonstrate any histoplasma. The successful culture of the fungus from bone marrow in which no organisms were recognized microscopically is the best evidence we have that this patient did have histoplasmosis. The lesions in the tissue are all so intimately associated with acid-fast bacilli there is no evidence any other causal agent was at work. It does not seem possible to decide whether this case represents a carrier state or if it is a matter of the histoplasma being present in the body without producing lesions. We know that the lesions of histoplasmosis can heal, but there is no evidence of more than one kind of process in the tissues of this case. We have seen at least one case of associated tuberculosis and histoplasmosis, and histoplasmosis has occurred with unusual frequency in association with other chronically debilitating diseases such as the malignant lymphomas; so it might be considered that the major part of the disease in this patient was tuberculosis with a coincidental infection with histoplasma which was not demonstrable terminally.

Final Anatomic Diagnoses: Miliary tuberculosis, caseous and fibrocaseous, involving the lungs, with tuberculous pneumonia in the lower lobe of the left lung; mediastinal lymph nodes, liver, spleen, adrenals, kidneys, and bone marrow; tuberculous pleurisy, right, and pericarditis; tuberculous pyelonephritis.

Acknowledgment: Illustrations were made by the Department of Illustrations, Washington University School of Medicine.

[6] Raftery, A. Subclinical histoplasmosis. *J. A. M. A.*, 145: 216–220, 1951.

Case Reports

Mobilization of Gouty Tophi by Protracted Use of Uricosuric Agents*

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New York, New York

It has been known for some time that salicylates effect a marked increase in urinary urate excretion when administered to gouty subjects in substantial dosage, about 5 gm. daily, particularly if given in conjunction with sodium bicarbonate or other alkalinizing agents.[1–5] More recently it has been found that carinamide (4′-carboxyphenylmethanesulfonanilide)[4–6] and benemid® (p-(di-n-propylsulfamyl)-benzoic acid)[4,5,7,8] also are potent uricosuric agents and are better tolerated, particularly benemid.[8] The increased urinary urate excretion produced by these drugs is generally attributed to suppression of tubular reabsorption of urate.

We have been exploring the usefulness of these uricosuric agents in the management of chronic gout with the hope that by maintaining augmented excretion of urate it might be possible to minimize deposition of urate in the tissues and thus obviate further development of the deformities and disabilities of chronic tophaceous gout. Our experience thus far indicates that this may be accomplished. Once the uricosuric regimen was fully established, no new tophi have appeared over months or years of observation in any of our patients with chronic tophaceous gout, including those patients in whom crops of new tophi had developed at relatively short intervals in the period immediately preceding initiation of therapy. Moreover, interruption of treatment was followed in some instances by resumption of overt new tophus formation within a few months.

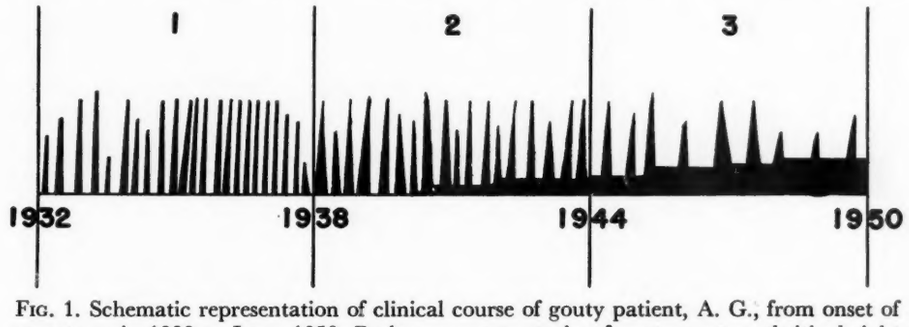

Fig. 1. Schematic representation of clinical course of gouty patient, A. G., from onset of symptoms in 1932 to June, 1950. Peaks represent attacks of acute gouty arthritis, height indicating the severity and width the duration of each episode. The solid baseline indicates increasing severity of persistent manifestations of chronic tophaceous gout. The course is divided into three phases of development.

Recently we have been obtaining evidence in some cases of reduction in size of long established tophi. The following instance is a case in point:

Case Report

A. G., a sixty-two year old male, was first seen in June, 1950, for gout of eighteen years' duration. His first attack of acute gouty arthritis in 1932 involved the right big toe and incapacitated him for only a few days. The subsequent development of the disease can be divided into

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three stages, each of approximately six years' duration. (Fig. 1.) From 1932 to 1938 he was subject to frequent attacks of podagra, which recurred at about monthly intervals, with no residual complaints between attacks. In 1933 he noted one small tophus on his right ear. In 1938 the episodes of acute gouty arthritis began to run a longer course, involving more joints and responding less readily and completely to colchicine. During this period the ankles, knees and elbows were frequently involved, leaving the toes relatively free. On many occasions several joints were swollen simultaneously. He also suffered recurrent attacks of acute olecranon bursitis, with serous effusions requiring repeated taps. In 1939 tophaceous deformities of the feet developed and slowly increased in size, initially at the first metatarsophalangeal joints, then at the fifth metatarsophalangeal joints and finally on the dorsum of the feet and about the ankle joints. In consequence he had more difficulty in walking and standing and was obliged to use oversize shoes. In 1945 a large tophaceous swelling appeared on the fourth finger of the left hand, together with a smaller tophus at the second metacarpophalangeal joint. About this time the serous effusions of the left olecranon bursa subsided, leaving a large permanent swelling. Since 1948 crops of small tophi had appeared in the lobes of both ears.

As a result of increasing disability due to chronic tophaceous gout, the patient had been unable since 1943 to carry on any regular work as a salesman. Treatment during this latter period consisted of colchicine, 1 mg., and aspirin, 0.65 gm., every night.

On examination in June, 1950, he presented the picture of advanced tophaceous gout. There were tophaceous deposits in both feet, especially around the metatarsophalangeal joints. These were firmly attached to the underlying bones. There were no discharging sinuses. One large tophus was palpable along the flexor tendons of the left ankle. The left elbow was the site of a solitary tophus about the size of a hen's egg. The proximal phalangeal joint of the left fourth finger was immobilized by a cherry-sized tophus; another was present at the second metacarpophalangeal joint of the left hand and a third large mass was palpable on the ulnar side of the left wrist. These tophi were firmly attached to the underlying joints. About six or seven small tophi were present in both ear lobes. Roentgenologic examination showed punched-out areas in the medial condyle of the humerus, the proximal and middle phalanges of the left fourth finger and the first metatarsophalangeal joints of both feet, with large soft tissue swellings around these areas. The knees, ankles, wrists, right hand and elbow showed no significant joint changes.

The serum urate consistently exceeded 11 mg. per cent. The mean urinary urate excretion on a low purine diet was 512 mg./24 hours. Red cell count was 4.12 million; hemoglobin 12.8 gm. per cent; white cell count and differential normal. ESR was 59 mm. in the first hour (Westergren). The urine showed 1+ albumin, with occasional granular and hyaline casts, and a few red blood cells and white blood cells. Serum NPN was 59 mg. per cent and PSP excretion 25 per cent in the first hour and 13 per cent in the second hour. Blood pressure was 140/80 mm. Hg.

On June 26, 1950, surgical excision of the tophus at the left elbow was attempted under local anesthesia. The major part of the tophus, which was quite vascular, was found to extend to and was attached to the articular capsule and the ulnar collateral ligament. About 10 gm. of the tophaceous mass was removed, leaving the greater portion behind. The wound healed well. Olecranon bursitis with serous effusion subsequently developed, requiring repeated aspirations. The urate content of the aspirated fluid was usually somewhat higher than that of the serum, sampled simultaneously.

Starting on June 29th the patient was given carinamide, 12 gm. a day for eighteen days, and then benemid, 2 gm. a day for eighty-four days. He was maintained on a low purine, low protein diet throughout this period. Prophylactic colchicine was continued. The mean daily urinary urate excretion on this regimen was 644 mg., a daily excess excretion of approximately 132 mg. Thus in a period of 102 days (from June 29th to October 8th) the total excess excretion was about 13.5 gm. The patient's serum urate level fell to 6.5–8.0 mg. per cent. Since he was still having a great deal of diffuse pain and stiffness in various joints, medication was changed on October 26th to sodium salicylate combined with sodium bicarbonate. It was found that with 3 gm. salicylate a day he was more comfortable but there was virtually no uricosuric effect with this dosage. Mild salicylism soon developed, with tinnitus, diminution in hearing and gastric irritation. Because of

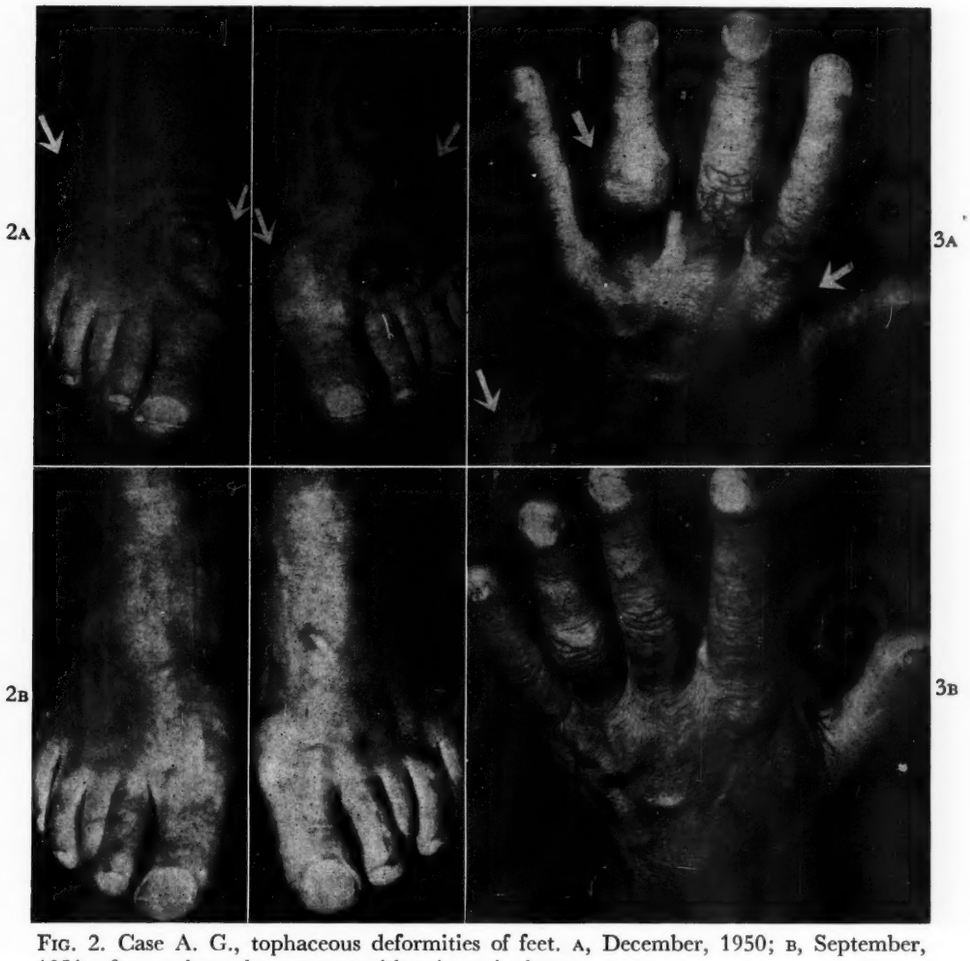
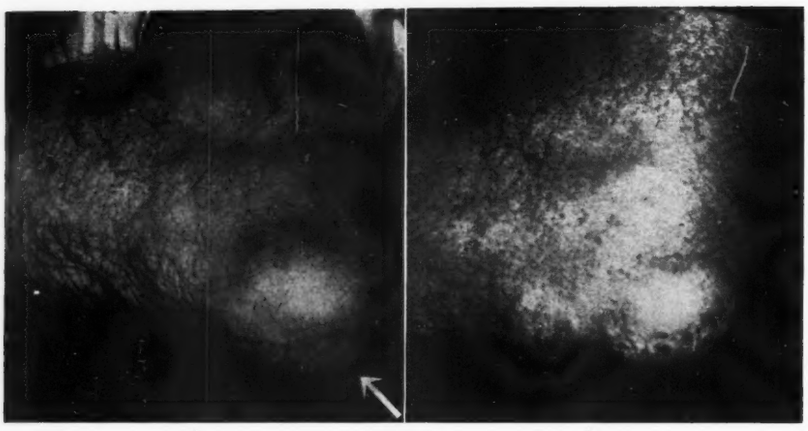


FIG. 2. Case A. G., tophaceous deformities of feet. A, December, 1950; B, September, 1951, after prolonged treatment with uricosuric drugs.
FIG. 3. Case A. G., tophaceous deformities of hands. A, December, 1950; B, September, 1951.

salicylism enteric-coated sodium salicylate was tried. The patient tolerated 4 gm. daily of the enteric-coated sodium salicylate very well and his diffuse joint pains disappeared almost entirely. On this dosage of salicylate his mean daily urinary urate excretion increased to 800 mg./24 hours, with an associated fall in serum urate to 6.0 ± 0.5 mg. per cent. The dosage of enteric-coated sodium salicylate was increased to 5.2 gm. a day on December 7th, a dosage which he tolerated well, and the diet was liberalized somewhat in respect to protein intake. His serum urate level then was maintained at 5.0–5.5 mg. per cent and there was a daily urinary excretion of 800 to 1,000 mg. for the next three months. Since March, 1951, the serum urate levels have remained within 4.0 ± 1.0 mg. per cent. The urinary excretion of urate has continued at levels of 700–800 mg. per twenty-four hours.

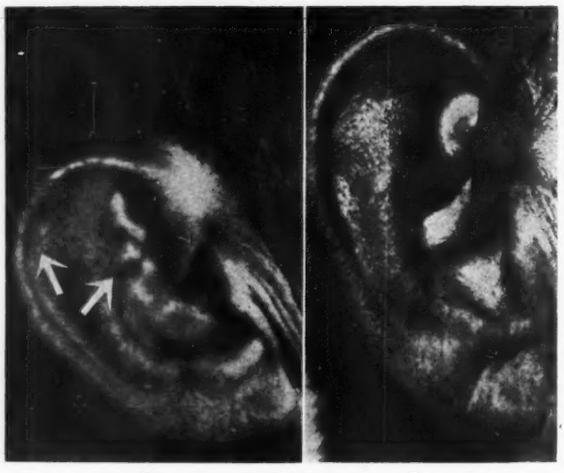
Figures 2A, 3A, 4A and 5A indicate the status of his visible tophi in December, 1950. Since institution of uricosuric therapy in June, 1950, no new tophi had appeared, nor was there any change in the established tophi. At the end of February, 1951, the patient began to note that his shoes were becoming too large and the number of tophi on his ear lobes was decreasing. By May the decrease in size of tophi became quite apparent and by September, 1951, the changes were quite striking. (Figs. 2B, 3B, 4B and 5B.) We estimate from the urinary urate determinations that an excess of 100 gm. of urate was mobilized and excreted during the period of uricosuric therapy.

At the time the photographs were taken in September, 1951, the serum urate was 3.3 mg. per cent and the urinary urate excretion was 700 mg. per day. Red blood count was 4.25 million; hemoglobin 13.5 gm. per cent; white cell count,



4A 4B

FIG. 4. Case A. G., tophaceous deformity of left olecranon bursa. A, December, 1950; B, September, 1951.



5A 5B

FIG. 5. Case A. G., tophi of left ear. A, December, 1950; B, September, 1951.

differential and platelets were normal. ESR was 23 mm. in the first hour. The urine still showed 1 + albumin; the sediment contained a few red cells and leukocytes but no casts. Serum NPN was 45 mg. per cent. The PSP excretion was 28 per cent in the first hour and 15 per cent in the second hour. Blood pressure was 160/90 mm. Hg. Prothrombin time was 14 seconds (normal, 12 seconds). Serum salicylate level was 20 mg. per cent.

The patient is much improved and now able to carry out part-time activities. Of interest is the fact that except for a minor acute attack of gout early in July, 1950, shortly after starting benemid therapy, and another in October, 1950, he has been free of acute gouty arthritis while receiving 1 mg. of colchicine daily for prophylaxis.

COMMENTS

Disappearance of established tophi as a result of treatment with uricosuric drugs, such as occurred in the case described, was not anticipated. It has always seemed likely that old urate deposits in the tissues are beyond the reach of humoral agents, and the minimal mixing of intravenously injected N^{15}-labeled uric acid with tophus content observed by Benedict et al.[9] appeared to confirm this belief. However, the observations in the case reported herein seem to be unequivocal (Figs. 2 to 5) and are supported by data indicating a markedly negative urate balance for about one year, with mobilization of approximately 100 gm. urate from the tissues. Presumably, mobilization of urate from the tissues is facilitated by the sharp reduction in serum urate level produced by these agents.

Sometimes tophi spontaneously decrease in size and disappear, particularly from the ear or elsewhere after breaking through the skin and discharging their contents. There was no spontaneous external evacuation of urate in the present instance nor have we encountered so general a spontaneous reduction of tophi anywhere in the literature, or in 270 unpublished case histories of gout we have reviewed, or in our personally supervised series of sixty gouty cases prior to treatment with uricosuric agents. There are, moreover, other instances of disappearance of tophi in our patients following prolonged administration of salicylates in 5 gm. daily dosage. Case V. P., who had very extensive and crippling urate deposits particularly in the hands, feet and olecranon bursae, has also noted unequivocal reduction in size of many tophi, with partial restoration of function of the

extremities. In this instance some 90 gm. of excess urate were mobilized and excreted in the urine over a period of six months. Case L. R. has observed virtual disappearance of a hen's egg size tophus of the olecranon bursa. Several patients on protracted benemid medication similarly have noted disappearance or decrease in size of tophi, for the most part small or recently established deposits, together with lessened swelling of chronically enlarged joints. This has been most striking in the feet, enabling these patients to walk better and to wear smaller sized shoes than they had been accustomed to for years. The results with benemid are particularly encouraging because very few of our patients have been able to tolerate for long the required dosage of salicylates, which in amounts less than 5 gm. per day usually has little or no uricosuric effect and in doses of the order of 2 gm. per day is apt to cause retention of urate.[1–5] Benemid ordinarily produces sustained uricosuria when given to patients with chronic gout in doses of 0.5 or 1.0 gm. per day, a dosage level of low toxicity.[8]

A matter of some concern in protracted treatment of chronic gout with uricosuric agents is the possibility of aggravating renal damage by increasing the excretory urate load on the kidneys. So far we have not observed any indication of this, provided dosage is carefully regulated according to the urinary urate level, and ample fluids and alkalinizing salts are given; in Case A. G., in fact, the serum NPN declined from 59 to 45 mg. per cent under treatment, perhaps reflecting mobilization of urate deposits in the kidneys. In any event, so far as can be determined these drugs do not cause any significant increase in the amount of urate formed in the body or any increase in glomerular filtration rate, but they apparently do suppress urate reabsorption in the tubules. The chief hazard in their use would therefore seem to be precipitation of urate in the collecting tubules and this apparently can be minimized by the precautions indicated. The evidence that uric acid has a direct "toxic" action in concentrations of the order of magnitude under consideration is unsubstantial.[10]

As indicated in the case report, it is our practice to institute a low purine, restricted protein diet in conjunction with uricosuric therapy in order to minimize urate production while augmenting urate excretion, so that maximal negative urate balance may be achieved. Even under these conditions mobilization of visible urate deposits is a slow process demanding the utmost patience and perseverance. Proper regulation throughout this period requires frequent determinations of serum and urinary urate levels, constant attention to diet and dosage levels of medication, and vigilant search for evidences of untoward side reactions.

SUMMARY

A case of advanced tophaceous gout exhibiting unequivocal reduction in size of many tophi in the course of protracted uricosuric therapy is described. It may be possible by proper use of uricosuric agents not only to minimize new tophus formation but also to cause the disappearance of old established tophi.

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Localized Amyloid Deposition in the Lower Respiratory Tract*

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We have recently had the opportunity to study a patient with amyloid infiltration of the trachea and main bronchi who was admitted to the hospital with the provisional diagnosis of bronchogenic carcinoma. The correct diagnosis was not suspected until the pathologist examined the bronchoscopic biopsy. We were therefore stimulated to review the literature for more information about the nature and frequency of this unusual lesion.

Local amyloid tumefactions confined to a single organ have been reported in the larynx,[1–7] urinary bladder,[8–11] conjunctiva,[12–14] mouth and nasopharynx[15–18] and a variety of other organs.[19–23] They have frequently been mistaken clinically for neoplasms. Local amyloidosis of the upper respiratory tract, especially the larynx, is more common than involvement of the lower respiratory tract including trachea, bronchi and pulmonary parenchyma. We were able to find twelve well documented cases and a questionable thirteenth case of local amyloid deposition in the lower respiratory tract in addition to our own case.

CASE REPORT

M. L. (Montefiore Hospital No. 50886), a forty-three year old white male house painter, entered Montefiore Hospital on May 5, 1950. He first noted wheezing and shortness of breath on effort five years before admission but attributed his complaints to exposure to paints. Shortly thereafter a cough developed which was productive of up to one-half cupful of thick white sputum daily. Despite progressively increasing symptoms including dyspnea at rest he continued to work until the winter of 1945 when he was admitted to a hospital for pneumonia of the left lower lobe from which he rapidly recovered. He returned to work and was comfortable during the following summer. Symptoms of dyspnea, wheezing and productive cough recurred with the onset of cold weather and persisted except for relatively asymptomatic intervals during the summer months. In the winter of 1948 he was again hospitalized for pneumonia, this time of the right lower lobe. Hemoptysis was noted for the first time on this occasion. Because of persistent right lower lobe consolidation bronchoscopy was advised but the patient refused consent. For the following fourteen months penicillin in oil was administered three times weekly and during this period he was well except for slight cough productive of a teaspoonful of sputum daily. During the winter of 1949 to 1950 there were two further episodes of penumonia characterized by acute onset of fever, chills, productive cough, dyspnea and hemoptysis. Thereafter the sputum became more copious, viscid and greenish yellow. The symptoms did not subside during a vacation in Florida. After the patient's return home x-ray examination on March 29, 1950, revealed a shadow extending from the left hilum into the left lower lung field. Hospitalization was advised.

On admission to Montefiore Hospital the patient was found to be a well developed, well nourished, sun-tanned white male of forty-three years who was dyspneic and orthopneic. Temperature was 99°F., pulse rate 72, respiration 38 and blood pressure 110/70. The pertinent physical findings were as follows: The trachea was in the midline. Wheezes were palpable over the entire left chest. On auscultation inspiratory and expiratory wheezes were audible over both lung fields and there were rales over the lower left chest posteriorly. The leafs of the diaphragm were normally mobile with respiration. The heart was not enlarged or otherwise remarkable. The abdomen was soft and presented no masses

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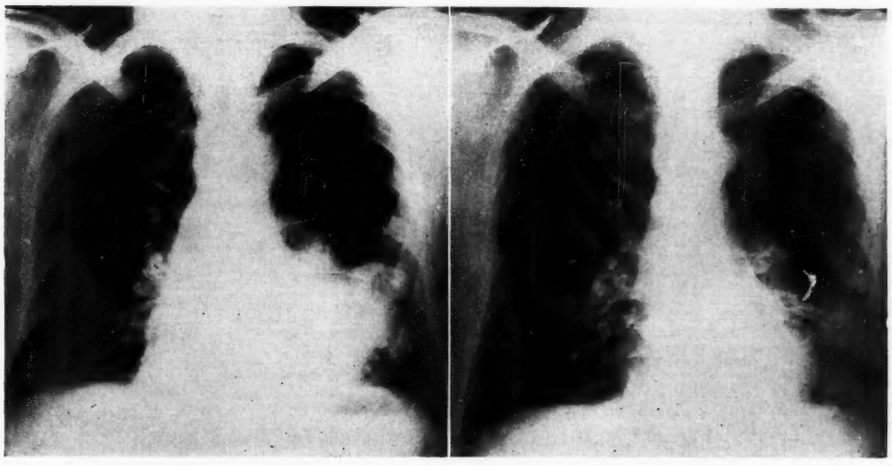

1A 1B

FIG. 1. A, Chest film May 8, 1950; B, chest film January 25, 1951

or palpable organs. Rectal examination revealed a slightly enlarged, smooth prostate. The extremities were normal and clubbing was absent. No bone tenderness was elicited.

The admission chest films of May 8th (Fig. 1A) revealed a large area of irregular density extending from the left hilar region out into the left middle and lower lung fields and involving the base of the left lower lobe as well as the lower portion of the left upper lobe from hilum to lingula.

Initial bronchoscopy was performed on May 10th and disclosed an extremely extensive lesion consisting of projecting masses extending in irregular fashion from the subglottic area down to the carina, which was considerably broadened, and further into both main bronchi. The masses varied from pea-sized, globular projections into the lumen preventing distant visualization to broad, flat elevations. The main bronchi, particularly the left, were quite narrowed by the flat elevations. The masses were covered by intact mucous membrane and were not particularly friable. They were firm and hard, and were bitten away by the biopsy forceps with considerable difficulty. Very little bleeding was encountered on removing the projections either on the first examination or on subsequent ones. The bronchoscopist's initial impression was "externally infiltrating and metastasizing carcinoma." The pathologist found no tumor but reported amyloid deposition in the submucosa of the trachea.

Intensive investigation disclosed no evidence of generalized amyloid disease. The blood protein was 6.8 gm. per cent, albumin 5.0 gm. per cent and globulin 1.8 gm. per cent. The Congo red test was negative (17 per cent removed after one hour). Bence-Jones proteinuria was absent. Marrow studies were negative for myeloma. A complete roentgenologic skeletal survey revealed no osseous abnormalities. Electrocardiograph was not remarkable.

The following additional laboratory studies were performed: Hemoglobin was 13.5 gm. per cent, red blood cells 4,170,000 per mm.,^{3} and white blood cells 7,400 per mm.,^{3} with a normal differential count. Urinalysis: specific gravity ranged from 1.012 to 1.022. All specimens were negative for sugar and albumin; sediments contained only occasional epithelial cells. Sputum smears and cultures were negative for acid-fast bacilli on three occasions. The Mazzini test was negative. Erythrocyte sedimentation rate was 9 mm. in one hour; fasting blood sugar 80 mg. per cent; blood urea nitrogen 8.0 mg. per cent; cephalin flocculation negative; thymol turbidity 1 unit; serum bilirubin 0.46 mg. per cent; cholesterol 254 mg. per cent.

Up to January 10, 1951, twelve additional bronchoscopies were performed to confirm the diagnosis and to remove the obstructing masses. Eleven biopsy specimens taken from the trachea and bronchi between May 10, 1950, and January 10, 1951, were available for review. Gross specimens varied in size from small, ruddy tissue masses less than 3 mm. in diameter to a mass of small fragments having an aggregate volume of 4 cc., the largest individual particle measuring 8 mm. in greatest dimension. Multiple sections of trachea and bronchi included only the mucosal and submucosal portions of the wall. (Fig. 2.)

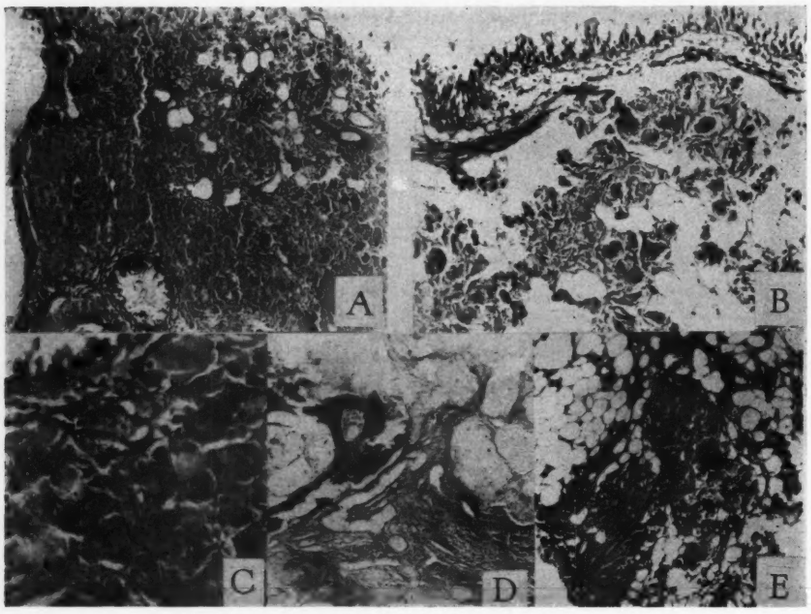

FIG. 2. A, Bronchial biopsy; amyloid deposition through entire tunica propria; mucosa on left; bronchial gland lower left corner (original magnification 105 ×). B, bronchus; mucosa of pseudostratified ciliated columnar cells; amyloid and fat in tunica propria (original magnification 255 ×). C, amorphous acellular hyaline amyloid in tunica propria; mucosa at upper left (original magnification 550 ×). D, metaplastic bone and cartilage in tunica propria (original magnification 85 ×). E, foci of adipose tissue adjacent to amyloid deposits in tunica propria (original magnification 105 ×).

The mucosa consisted of a pseudostratified columnar ciliated epithelium with occasional goblet cells resting on a thick basement membrane. Beneath the mucosa were irregular masses and clumps of amorphous hyaline material which stained pink-red with hematoxylin-eosin, bright orange with various lots of Congo red, and purplish red with metachromatic dyes such as crystal and methyl violet. All stains for amyloid were confirmed on fresh frozen sections. Unequivocally positive reactions for amyloid were obtained on each of the eleven submitted specimens. Interspersed amidst the amyloid masses were occasional normal tracheal and bronchial glands, small irregular islands of metaplastic cartilage, a solitary focus of metaplastic bone with hematopoietic tissue within its medullary space and areas of mature adipose tissue. No giant cells were found.

The patient was treated by piecemeal removal of the obstructing nodular masses using an ordinary Yankauer type of bronchoscopic cutting biopsy forceps. The largest masses were in the upper and lower trachea. At first bronchoscopy was performed weekly, later every two weeks and, since hospital discharge on July 28, 1950, approximately every month. Following each bronchoscopic removal of tissue there was subjective and objective improvement. After ten bronchoscopies the patient could comfortably perform a day's work. He still has a morning cough productive of yellowish sputum which is blood tinged on rare occasions, usually during the week following a bronchoscopy. He is no longer dyspneic on rest or ordinary activities. Wheeze is less prominent both subjectively and objectively. It is noted by the patient only after walking rapidly up two flights of stairs and during sexual intercourse. Repeated chest films from May 3, 1950, to November 25, 1950, demonstrated no remarkable change in the infiltration of the left lung. However, in the interval from November 25, 1950, to January 25, 1951, very appreciable resolution of the pulmonary density occurred. (Fig. 1B.)

Removal of the amyloid by forceps is still in progress but the therapeutic plan may include an attempt at further enlargement of the airway, particularly the lower bronchi, by electrocoagulation. It has been interesting to note that there has been little or no increase in size of the flat lesions. It has therefore been possible to keep

ahead of any growth of the lesions and to improve the airway even with therapy at monthly intervals.

COMMENTS

In Table 1 we have tabulated certain of the recorded data available from the thirteen[24–36] previously recorded cases and from our case.

TABLE 1

Case	Author	Age	Sex	Duration of Symptoms Prior to Diagnosis	How Diagnosed	Associated Pathologic Condition	Location of Amyloid
1	Balser[24]	66	M	19 yr.; "bronchitis" with evidence of progressive bronchostenosis	Autopsy	Chronic bronchiectasis and pneumonitis of R.U.L.; several ossified areas in right lung	Trachea and main bronchi
2	Kraus[25]	..	M	None recorded	Autopsy	Pulmonary emphysema and malnutrition; acute pneumonia	Trachea
3	Manasse[26]	63	M	None recorded	Autopsy	Perforated duodenal ulcer with generalized peritonitis	Larynx and trachea
4	Glockner[27]	76	M	None recorded	Autopsy	B.P.H.; cystitis, hydronephrosis and pyelonephritis	Larynx, trachea and main bronchi
5	Johanni[28]	66	F	15 mo.; hoarseness, cough; later progressive dyspnea	Autopsy	Incomplete description of associated pathologic condition	Larynx and trachea
6	Herxheimer[29]	65	M	40 yr.; hoarseness	Autopsy	Abscess of R.L.L.; right empyema	Larynx, trachea and lung
7	von Werdt[30]	71	M	6 yr.; intermittent hoarseness; in last year dyspnea with stridor	Surgical removal of tumor; autopsy 11 hr. postoperatively	Bronchiectasis R.U.L. and R.M.L.	Larynx, trachea and main bronchi
8	Meyer[31]	57	M	None recorded	Autopsy	Chronic interstitial nephritis, arteriosclerosis, early cirrhosis of the liver, fresh cerebral hemorrhage	Lung
9	Hallermann[32]	52	F	None recorded	Autopsy	Postoperative pneumonia of R.L.L., R.M.L., L.L.L.; right empyema; thoracotomy	Lung
10	Bauer[33]	30	M	1 yr.; dyspnea and hoarseness	Laryngoscopy with biopsy	Goiter	Larynx and trachea
11	Bloch and Soulas[34]	46	F	4 mo.; cough, increasing dyspnea and hoarseness	Bronchoscopy with biopsy	None described	Larynx and trachea
12	Falconer[35]	71	M	2 mo.; increasing dyspnea	Autopsy	Gastric ulcers; hepatic cirrhosis with esophageal varices	Trachea and main bronchi
13	Weismann et al.[36]	35	M	9 yr.; cough and intermittent hemoptysis	Right pneumonectomy	Pneumonitis R.L.L. and R.M.L.	Right main bronchus and branches
14	Authors' case	43	M	5 yr.; cough, dyspnea, wheezing	Bronchoscopy with biopsy	Pneumonic infiltration L.L.L. and L.U.L.	Trachea and main bronchi

Age Incidence. Amyloid deposition in the lower respiratory tract is apparently a disease discovered in later adult life, nine of the fourteen patients being over fifty, with one case in which the age was not stated. The youngest patient was thirty years of age, the oldest seventy-six.

Sex Incidence. Males predominated in this group in a proportion of eleven to three. This differs from primary systemic amyloidosis, Eisen[37] having reported twenty-six males and twenty-two females in the cases collected by him.

Clinical Features. The duration of recorded symptoms was quite variable in the cases reviewed. In Case 12 there was two months of increasing dyspnea until death. In Case 6 hoarseness was present for forty years. The clinical picture is extremely variable and is dependent upon the exact location and extent of the amyloid deposition. When the deposition is small in amount or located in silent areas, no symptoms develop. Thus in Case 2 presenting only a bean-sized submucous nodule in the posterior tracheal wall and in Cases 8 and 9 in which amyloid masses were confined to the pulmonary parenchyma the diagnoses were made as incidental findings at autopsy after death due to unrelated major disease.

When the larynx is involved in addition to the lower respiratory tract, as occurred in five instances (Cases 5, 6, 7, 10 and 11), hoarseness is a prominent symptom. Involvement of the larynx alone is not within the scope of this review and has been extensively reviewed elsewhere. Patients in this older age group with persistent hoarseness may be suspected of having laryngeal carcinoma.

Symptoms and signs resulting from involvement of the trachea and bronchi are expressions of the amount of obstruction produced. One may therefore encounter various degrees of dyspnea, cough and wheezing with the superimposition at times of the features of acute recurrent pneu-

monia or chronic bronchiectasis. It is in this type of involvement that the diagnostic possibilities will be diverse and will run the gamut of asthma, foreign body, unresolved pneumonia, tuberculosis, bronchiectasis, adenoma and carcinoma.

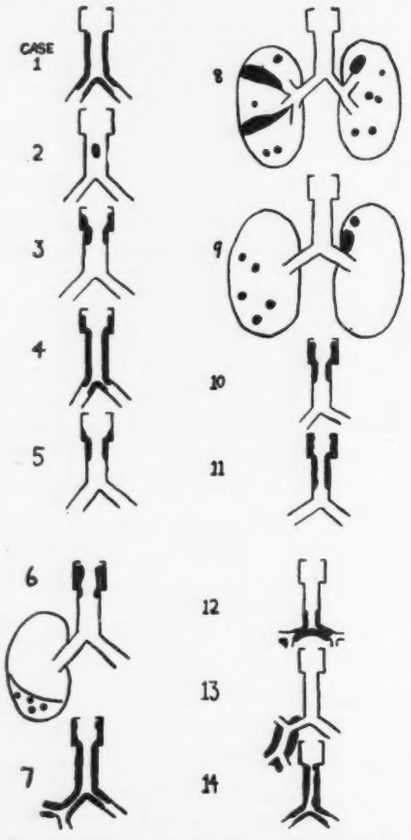

FIG. 3. Schematic representation of the location and extent of the amyloid deposits in fourteen cases of amyloidosis of the lower respiratory tract.

Diagnosis of this condition is almost completely dependent upon pathologic study of biopsy material. The lesion is so uncommon that on gross inspection alone no observer would venture the diagnosis. As has been mentioned, in our case the initial gross impression on bronchoscopy was infiltrating carcinoma of the submucosally infiltrative type. When viewed in retrospect certain features speak against such a diagnosis. These include (1) the unusual extent of the lesion throughout the entire trachea, carina and both major bronchi, (2) the intact mucous membrane, (3) the firm, tough consistency of the masses and their unusual resistance to the cutting forceps and (4) the paucity of bleeding on removal of the masses. It is difficult to imagine any disease other than infiltrative carcinoma from which this condition of amyloid deposition would require differentiation on the basis of bronchoscopic appearance. The appearance is almost unique and does not resemble that of Boeck's sarcoid, tuberculosis or any of the lymphomatous diseases.

Pathologic Features. Distribution of lesions: The distribution of amyloid in the reported cases is summarized below from Table I.

No. of Cases	Location of Amyloid
4	Larynx and trachea
2	Larynx, trachea and main bronchi
1	Larynx, trachea and lung
1	Trachea alone
3	Trachea and main bronchi
1	Right main bronchus
2	Lung (1 questionable)

The extent of involvement is shown schematically in Figure 3.

The absence of amyloid elsewhere in the body was confirmed by autopsy in eleven cases. The remaining three patients (Cases 11, 13 and 14) were alive at the time of publication of the case reports. In these cases there was no clinical or laboratory evidence of more generalized amyloidosis.

In all but one of the cases of tracheobronchial deposition amyloid was present within the submucosa and would have been available for bronchoscopic biopsy. In Case 13 if a biopsy had been obtained it would not have revealed the amyloid which was deposited in the external connective tissue coats around the right main bronchus and its branches, around the right pulmonary artery and inferior pulmonary vein.

Staining properties: As one of his five criteria for "atypical amyloidosis" Lubarsch[38] cited the variability of reaction with amyloid stains. Reference to Table II which summarizes the published data on staining reactions in the reported cases indicates that they conform in large measure to this generalization. The reports of Cases 10 and 11 did not include specific descriptions of staining properties. In both instances the pathologic description was "local amyloid," presumably on the basis of positive specific stains. Case 9 is questionable because of consistently negative staining reactions. It should be emphasized, however, that in the remaining eleven cases there were specific descriptions of at least one acceptable staining reaction identifying the material as amyloid. Perhaps too much emphasis has been placed on atypical staining

as a criterion of so-called atypical, primary or local tumor-forming amyloidosis.

Secondary changes within the amyloid tumefactions: Among the most conspicuous of the incidental changes associated with amyloid tumors of the lower respiratory tract are calcification and metaplastic bone formation. Calcification, ossification or both was described in ten of the twelve cases in which the pathology was given in detail. Similar changes are not uncommon in bronchial adenomas but are quite rare in carcinoma of the lung.

The occurrence of amyloid within the tracheal adipose tissue was noted in our case as well as in Case 3. In Case 7 amyloid was deposited in the peritracheal and hilar adipose tissue.

Giant cells were not encountered in our material but were noted as a conspicuous element in Cases 5, 6, 7, 8 and 10. Only in Case 5 did the author report the presence of amyloid substance within giant cells.

TABLE II

Case	Iodine	Iodine and H_2SO_4	Methyl Violet	Gentian Violet	Congo Red
1	Positive	Variable		Positive (variable)	
2	Inconclusive	Variable	Positive		
3	Positive			Positive	
4	Positive (not uniform)	Variable	Positive		
5	Positive	Variable	Positive		
6*	Positive	Positive	Positive		
7*	Positive	Inconclusive	Negative	Negative	
8* Small masses	Positive			Positive	
Large masses	Positive			Negative	
9	Negative		Negative	Negative	Negative
10	Reported as local amyloid; staining reactions not given				
11	Reported as local amyloid; staining reactions not given				
12			Positive		
13	Negative (gross)		Positive (not uniform)		Positive (not uniform)
14			Positive		Positive

* Also positive van Gieson's stain

SUMMARY AND CONCLUSIONS

1. A case of local amyloid tumefaction of the trachea and major bronchi is described. The condition was diagnosed by bronchoscopic biopsy and treated palliatively by periodic removal of amyloid masses.

2. Attention is called to this clinical entity in the differential diagnosis of stenotic lesions of the lower respiratory tract.

3. The clinical and pathologic features of thirteen previously reported cases and our fourteenth case are reviewed and tabulated.

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AUTHOR INDEX VOLUME XI

SUBJECT INDEX VOLUME XI

(ab.) = Abstract; (CPC) = Clinico-pathologic Conference; (E.) = Editorial

The American Journal of Medicine

Volume XI
JULY TO DECEMBER
1951

THE AMERICAN JOURNAL OF MEDICINE, INC.
NEW YORK MCMLI

CONTENTS OF VOLUME XI

ORIGINAL ARTICLES

Printed in the United States of America

Prelude to asthma?

not necessarily . . .

Tedral, taken at first sign of attack, often forestalls severe symptoms.

in 15 minutes. . . Tedral brings symptomatic relief with a definite increase in vital capacity. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

for 4 full hours. . . Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

Prompt and prolonged relief with Tedral can be initiated any time, day or night, whenever needed without fear of incapacitating side effects.

Tedral provides:

theophylline	2 gr.
ephedrine	3/8 gr.
phenobarbital	1/8 gr.

in boxes of 24, 120 and 1000 tablets

Tedral

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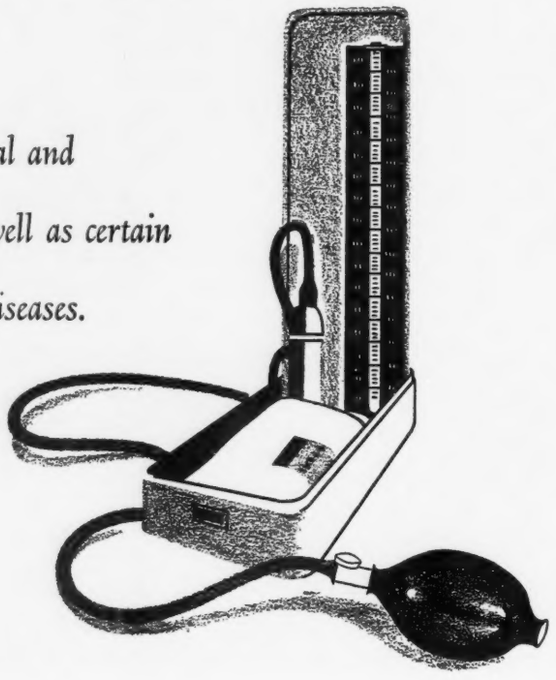
AUREOMYCIN

Hydrochloride Crystalline

Effective against many bacterial and rickettsial infections, as well as certain protozoal and large viral diseases.



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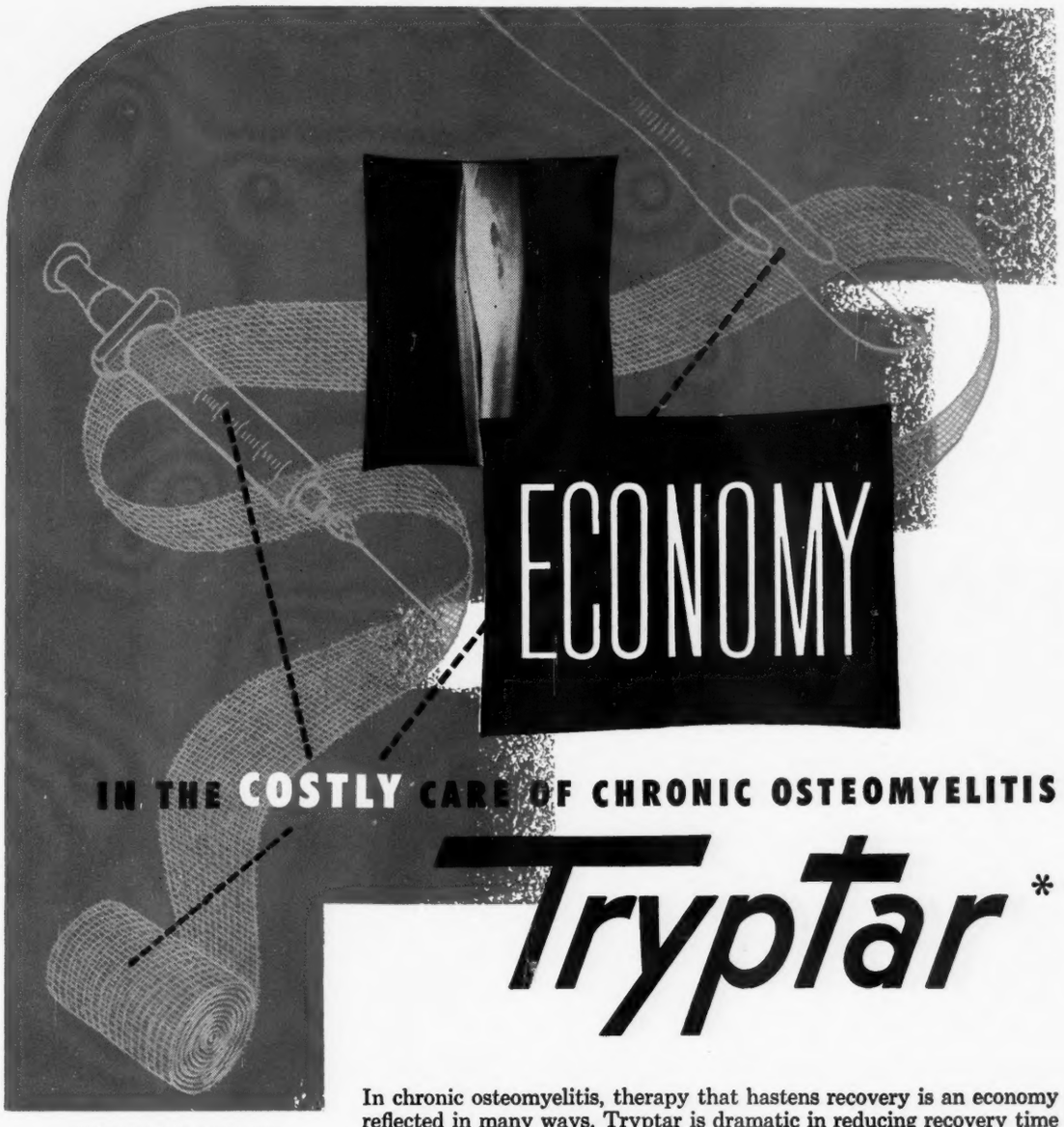

ECONOMY

IN THE COSTLY CARE OF CHRONIC OSTEOMYELITIS

Tryptar*

In chronic osteomyelitis, therapy that hastens recovery is an economy reflected in many ways. Tryptar is dramatic in reducing recovery time from years to months or even weeks.

Tryptar, selectively, causes dissolution of necrotic tissue and removes debris without injury to normal tissue. With topical administration, Tryptar is non-toxic and completely non-antigenic.

Tryptar in the treatment of osteomyelitis may be applied in the form of dry powder, in wet dressings, in gelatin capsules or by irrigation, depending upon the location of the lesion.

Tryptar is supplied as a two vial preparation: one 30 cc. vial contains 250,000 Armour Units (250 mg. of Tryptic Activity) of highly purified crystalline trypsin; the companion 30 cc. vial contains 25 cc. of Tryptar Diluent (Sorensen's Phosphate Buffer Solution) pH 7.1. Plus plastic adapter for use with powder blower.

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Crystalline Terramycin Hydrochloride Oral Drops provide 200 mg. per cc., 50 mg. in each 9 drops—the only broad-spectrum antibiotic available as a liquid concentrate affording optimal convenience and flexibility in dosage schedules.

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Terramycin Oral Drops are miscible with most foods, milk and fruit juices; can be taken "as is" or mixed. Potent oral drops offer rapid broad-spectrum antibiotic activity in a form permitting the utmost simplicity in the therapeutic regimen.

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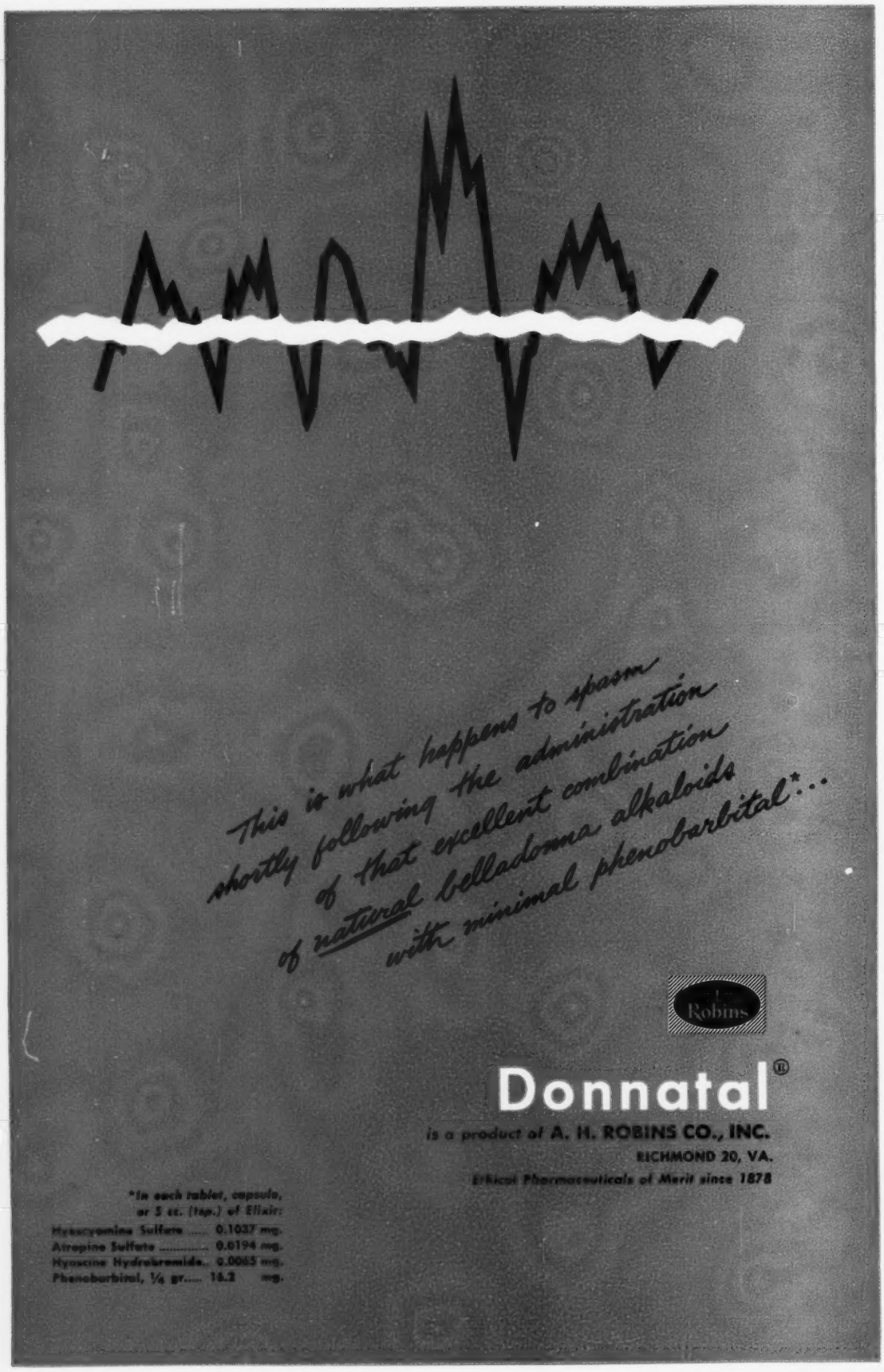
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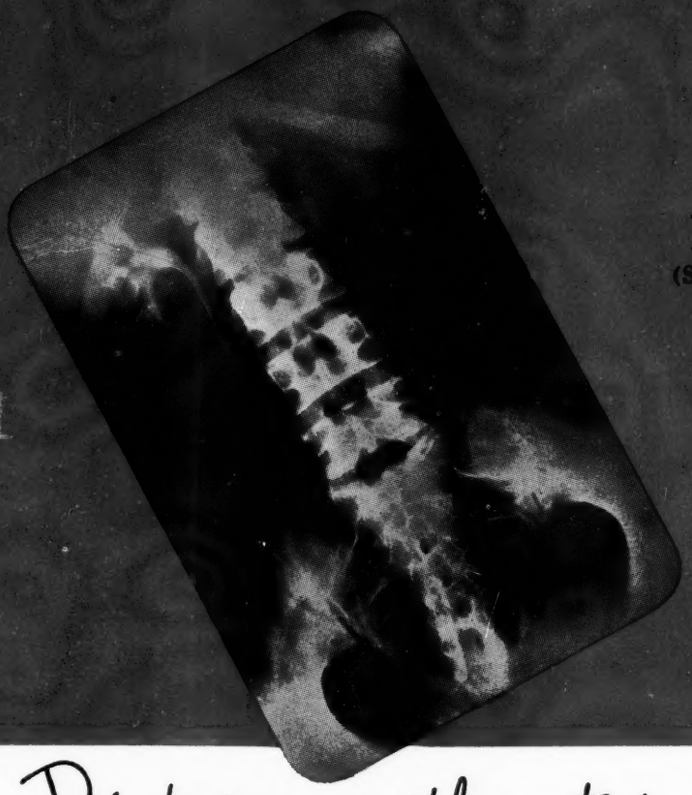

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A well tolerated cholecystographic agent, conveniently administered, pleasant to take.

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RUBRAGRAN FORMULA	1 capsule supplies	1 capsule t.i.d. supplies
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"Good to excellent results with PROTAMIDE"

. . . In 28 Cases of HERPES ZOSTER at Bethesda Naval Hospital*

William C. Marsh, Commander (MC) U.S.N., in a currently published paper[1], "Treatment of Herpes Zoster with Protamide," now available to physicians as a reprint, presents these findings:

"Thirty-one cases of herpes zoster were treated with Protamide. Good to excellent results were obtained in twenty-eight. In those failing to respond other factors besides age of patient may have been involved.

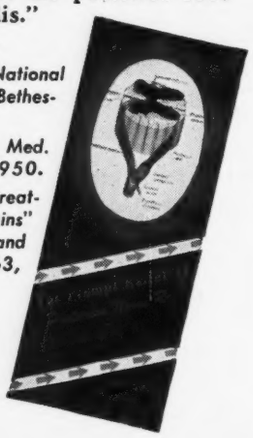
"No controls were in our study as thousands of intramuscular injections of other drugs given to patients with herpes zoster in the past, with no appreciable benefit, would adequately serve as a control.

"Pain, not merely the discomfort or itching, was the indication for treatment. Protamide (1.3 cc, the contents of one ampul) was given daily intramuscularly. No other local or systemic medications were given.

"The relief of pain was superior to that obtained when using either pituitrin, thiamine chloride, autohemotherapy, sodium iodide, or high voltage Roentgen therapy.

"The advantages of Protamide are the simplicity and absence of pain in administration, lack of reactions, and apparent safety.

"Costello[2] found that Protamide was effective in the relief of the posterior root pain of tabes dorsalis."



* *U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland.*

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patient in

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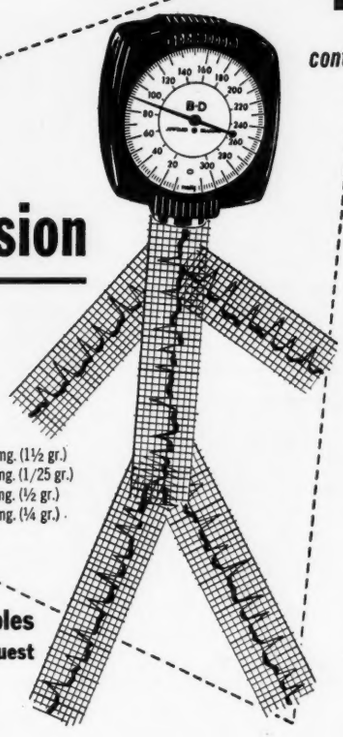

controls pressure and symptoms that send pressure soaring

more normal pressure
around the clock with two potent vasodilators.

eases stress on heart
by decreasing peripheral resistance.

relieves gastro-intestinal spasm
pain and other discomforts which aggravate pressure.

relaxes patient
mentally, physically; allays tension, worry, restlessness, insomnia.

from the first day of PERTENAL
therapy the whole patient is more comfortable, happier; able to live a more normal, perhaps longer life.

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Homatropine Methyl Bromide.	2.5 mg. (1/25 gr.)
Mannitol Hexanitrate	30 mg. (½ gr.)
Phenobarbital	15 mg. (¼ gr.)

PERTENAL samples on request

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In Corpus Luteum Hormone Deficiencies...

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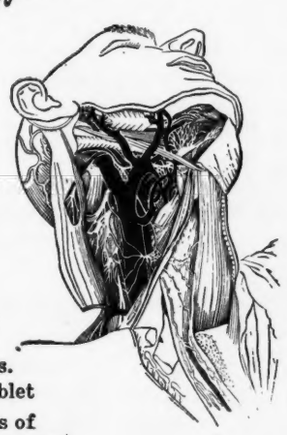

Progesterone in tablets specially prepared for sublingual or buccal administration and eminently suitable for oral (swallowed) use

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Bottles of 50, 100, 1,000

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"The observation of greatest importance in this investigation is that the results indicate that progesterone itself is active when administered by the oral (swallowed) route. Furthermore, progesterone itself appears to be more active orally than anhydroxyprogesterone." — Bickers, W.: J. Clin. Endocrinol. 9:8, 1949.

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In its widely distributed leaflet No. 268, "Eat a Good Breakfast," the U. S. Dept. of Agriculture states: "Summer or winter, there's something hot, as a rule, in a good breakfast.... Something hot is cheering and tones up the whole digestive route."

The problem of encouraging children to eat an adequately protective breakfast finds easier solution when Ovaltine in hot milk is recommended as a breakfast beverage. Many children clamor for a hot drink at the morning meal, and hot Ovaltine is the right kind of drink to recommend.

A cup of hot Ovaltine makes an excellent contribution of virtually all essential nutrients, adding substantially to the nutritional start for the day. It also serves in a gustatory capacity by enhancing the appeal of breakfast and making other foods more inviting.

The nutrient contribution made by a cup of Ovaltine is apparent from the table below. Note the wealth of essentials added to the nutritional intake by making the simple recommendation of adding a cup of hot Ovaltine to the child's breakfast.

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Ovaltine

Here are the nutrients that a cupful of hot Ovaltine, made of ½ oz. of Ovaltine and 8 fl. oz. of whole milk,*provides:

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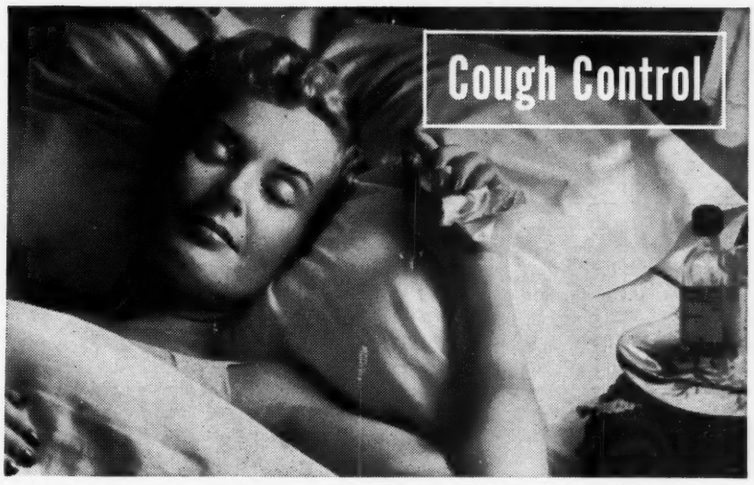
FAT	10.5 Gm.	COPPER	0.2 mg.	VITAMIN C	10 mg.
CARBOHYDRATE	22 Gm.	VITAMIN A	1000 I.U.	VITAMIN D	140 I.U.
CALCIUM	370 mg.	VITAMIN B_1	0.39 mg.	CALORIES	225
PHOSPHORUS	315 mg.	RIBOFLAVIN	0.7 mg.		

*Based on average reported values for milk.

Up-to-Date Antitussive



Sedative-antitussive effects of Methajade control sleep-robbing paroxysmal cough—allow patients to get needed rest.

SUBDUES VIOLENT COUGHING

METHAJADE® spares your patients the needless violence of exhausting, "unproductive" cough—without depriving them of the benefits of normal expectoration.

Because it contains *methadone*, the synthetic analgesic-antitussive, METHAJADE is capable of suppressing the irritability of the cough reflex without blocking it entirely.

Because it contains potassium citrate and diluted phosphoric acid, METHAJADE promotes the liquefaction and loosening of mucus, facilitating the expulsion of bronchial exudate and debris.

Because it relaxes smooth muscle, including that in the tracheobronchial tree, METHAJADE is effective in relieving the bronchial spasm often associated with coughs.

Together, these actions tend to *decrease* the frequency and *increase* the efficiency of coughing, and to relieve bronchial spasm. METHAJADE is therefore well qualified as a practical aid in achieving the modern objectives of cough control:

(1) *to* preserve *the natural physiologic benefits of the cough—*
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Composition—METHAJADE is a sugar-free antitussive with a delicious, fresh, lime flavor. Each 30 cc. (1 fl. oz.) contains:

Methadone hydrochloride* ..... (*d,l*-6-dimethylamino-4,4-diphenyl-3-heptanone hydrochloride) WARNING: may be habit forming.	10 mg.
Propadrine®, phenylpropanolamine hydrochloride	0.12 Gm.
Potassium citrate	1.2 Gm.
Diluted phosphoric acid	4.5 cc.
Alcohol 5%	

Average Dose for Adults: 1 to 2 teaspoonfuls every three or four hours.

CHILDREN:
(*note:* METHAJADE *should not be administered to children under 2 years of age. In children 2 years of age or older,* METHAJADE *should be used only in cases of severe, intractable cough.*)
Two years: ¼ teaspoonful not more often than every four hours.
Five years: ½ teaspoonful not more often than every four hours.
Ten years: 1 teaspoonful not more often than every four hours.

Packaging—METHAJADE is supplied in pint Spasaver® bottles and gallon bottles.
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**The analgesic potency of methadone hydrochloride is—weight for weight—approximately equivalent to that of morphine. It controls cough as well as, or better than, codeine. Methadone hydrochloride is subject to the provisions of the Harrison Narcotic Act.*

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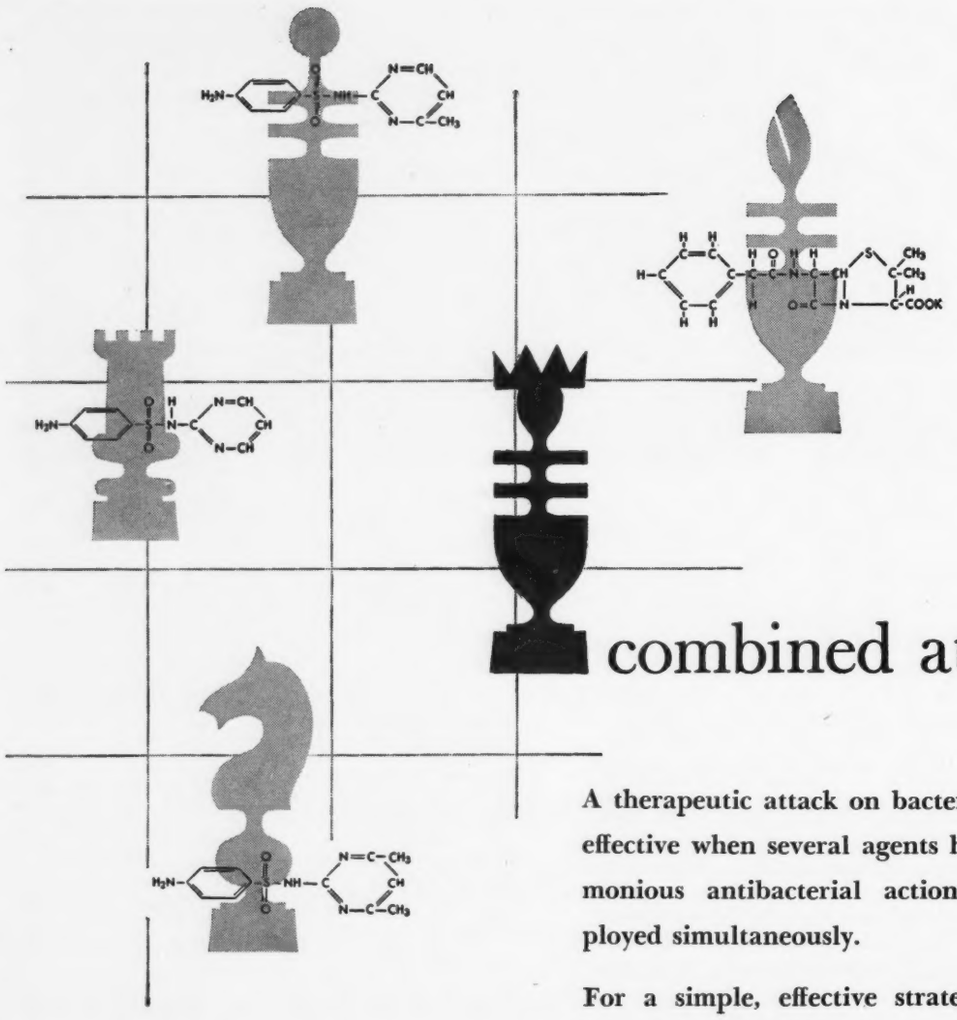

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A therapeutic attack on bacteria is more effective when several agents having harmonious antibacterial actions are employed simultaneously.

For a simple, effective strategy against susceptible organisms:

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Bottles of 50 and 500 tablets.

Each tablet contains:

Penicillin G Potassium, Crystalline	**100,000 units**
Sulfadiazine	**0.167 Gm.**
Sulfamerazine	**0.167 Gm.**
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new, non-barbiturate hypnotic

for safe, sound sleep
without drug hangover
free from habit-forming properties
of the barbiturates

safe
free from habit-forming or addiction properties of barbiturates; rapidly metabolized; no cumulative action; no toxic effects on prolonged use

acts gently and quickly in insomnia
mild hypnotic action quickly induces restful sleep

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no drug hangover
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DORMISON **is a substance new to pharmacology, completely different from barbiturates and other hypnotics. It contains only carbon, hydrogen and oxygen. It has no nitrogen, bromine, urea residues, sulfone groups or chemical configurations present in depressant drugs now in use.**

The usual dose of DORMISON (methylparafynol†) is one or two capsules, taken just before the patient is ready for sleep. DORMISON's wide margin of safety allows liberal adjustment of dosage until the desired effect is obtained. DORMISON is supplied as 250 mg. soft gelatin capsules in bottles of 100.

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ATHEROSCLEROSIS ?

Too Much Cholesterol or Too Little Phospholipids !

Plasma Ratio: $\frac{\text{PHOSPHOLIPID mg. \%}}{\text{CHOLESTEROL mg. \%}}$

The ratio is usually less than 1.0 in atherosclerosis; but in good health is 1.0 or more. 1 and 2

INCREASE PHOSPHOLIPIDS

The new isotope technique[3] has demonstrated that:

(a) choline deficiency occurs in man;

(b) phospholipid production is increased in deficiency states by choline;

(c) individuals differ in choline needs;

(Inositol also enters into synthesis of certain phospholipids.[4])

DECREASE CHOLESTEROL

Although cholesterol plasma levels may not be affected by dietary restrictions, the physical state of the cholesterol may be affected. Thus, "giant cholesterol molecules" associated with atherosclerosis may be eliminated by dietary control.[5]

RATIONAL MEASURES

In the light of these recent studies, *adequate* lipotropic therapy and cholesterol-restricted diets are rational measures in:

ATHEROSCLEROSIS
CORONARY ARTERY DISEASES
DIABETES
And Other Unbalanced Conditions of Disturbed Cholesterol Metabolism

GERICAPS

Supply Therapeutic Dosage of Lipotropics (700 mg.) with Vitamin A and B Complex factors to help compensate for deficiencies of low-cholesterol diets with Rutin and Vitamin C to prevent the retinopathy often associated with above diseases.

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BIBLIOGRAPHY

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[2]Gertler, M.M.; Stanley M.; Blund, E.F.; Age, Serum, Cholesterol and Coronary Artery Disease. Circulation 2:517 (1950)

[3]Science 109:613 (June 17) 1949

[4]Biochem. J. 40:494 (1946)

[5]Gofman, J.W.; et al.; Science. 111:166 (1950)

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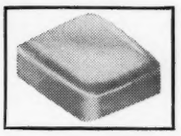

In a delicious hard candy base that completely masks antibiotic taste.

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1. Eagle, H., and Fleischman, R.: Proc. Soc. Exper. Biol. & Med. *68*:415, 1948
2. Bachman, M. C.: J. Clin. Invest. *28*:864, 1949

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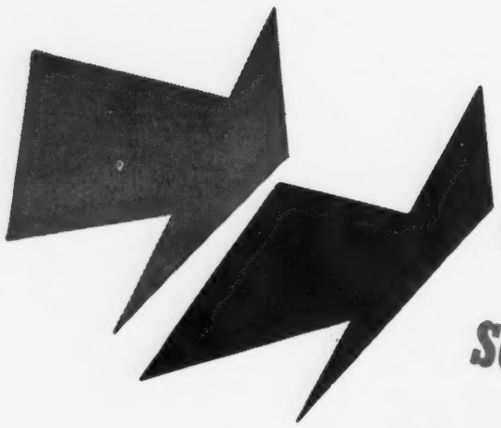

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sodium follows

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effective, well tolerated ...
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Editorial: J.A.M.A. *135*:576,
Nov. 1, 1947.

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Griggs, D. E., and Johns, V. J.:
California Med. *69*:133, Aug. 1948.

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December, 1951